FOCALIN™ PRODUCT MONOGRAPH

Short-Acting

Focalin™ CII

dexmethylphenidate HCl tablets

2.5 mg, 5 mg, 10 mg

FOCALIN™ PRODUCT MONOGRAPH

Short-Acting

Focalin™ C

dexmethylphenidate HCl tablets

2.5 mg, 5 mg, 10 mg

Contents

Introduction

Dexmethylphenidate hydrochloride (Focalin™), a twice-daily central nervous system stimulant, is a chemically refined form of *dl-threo*-methylphenidate hydrochloride (Ritalin®) indicated for the treatment of attention deficit hyperactivity disorder (ADHD).

The efficacy of Focalin in the treatment of ADHD was established in 2 controlled trials of patients aged 6 to 17 years who met ADHD criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*.[1]

Background of Focalin

Focalin is the single-isomer form of *dl-threo*-methylphenidate hydrochloride, or Ritalin, which is manufactured by Novartis Pharmaceuticals Corporation (East Hanover, New Jersey). Ritalin has been available in the United States since 1955 and has been indicated for the treatment of ADHD since 1961.[2] Taken 2-3 times daily or in multiple doses, Ritalin has demonstrated efficacy in the management and treatment of ADHD, and its safety in ADHD populations is well established.[3]

Methylphenidate is the most studied and currently is the most prescribed medication for the management of ADHD.[4] For many, Ritalin is considered the drug of choice.[5]

The Need for a Refined Drug

Ritalin is an asymmetric molecule made up of isomers that are mirror images of each other.[2] Stereoisomers have essentially identical physical and chemical properties, yet often different pharmacokinetic properties (absorption, distribution, biotransformation, and excretion). In 1992, the Federal Food and Drug Administration (FDA) highly encouraged the development of single-isomer drugs.[6]

Single-Isomer Drugs. The resulting transition to single isomers from racemic drugs clearly illustrates how drugs that are good enough to gain drug approval can still be further improved. In some cases, the effects of an isomer can be even more pronounced than those of its racemate. For example, esomeprazole magnesium for gastroesophageal reflux disease and the antibacterial, levofloxacin, are single-isomer products.

In the case of Ritalin, the isomers do not have equal activity. The *l* isomer is rapidly metabolized and degraded following oral administration and has little, if any, pharmacologic activity, whereas the *d* isomer is primarily responsible for the pharmacologic activity of Ritalin and other standard methylphenidate formulations.[7]

Benefits of Focalin

Focalin is a commercially available preparation that contains only the *d* isomer of methylphenidate—consistent with the FDA's call to action. Because this chemically refined form of Ritalin only contains the active isomer, it provides efficacy at half the dose of the racemic drug, methylphenidate (Table 1). Like other short-acting methylphenidate preparations, Focalin has a rapid onset of effect.[2] It is recommended that individual daily doses be administered at least 4 hours apart. Favorable efficacy, safety, and tolerability profiles have been demonstrated in well-controlled trials of Focalin (see Focalin Prescribing Information, Efficacy and Safety).

Table 1. Recommended Conversion Doses

Methylphenidate Dose	Focalin
5 mg	2.5 mg
10 mg	5 mg
20 mg	10 mg

The Importance of Comprehensive Treatment

Focalin is indicated as an integral part of a total treatment program for ADHD in children 6 years of age and older and may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for everyone with ADHD.[1]

Overview of Attention Deficit Hyperactivity Disorder

Etiology

The causes of ADHD are unknown. After years of research and experience, knowledge about its causes remains largely speculative. Most children with the disorder do not show evidence of gross structural damage in the central nervous system. Possible contributory factors include prenatal toxic exposures, prematurity, and prenatal mechanical insult to the fetal nervous system. There is also some evidence for a genetic basis for ADHD. For example, siblings of hyperactive children have about twice the risk of having the disorder compared with the general population. Also, biological parents of children with the disorder have a higher risk for ADHD than do adoptive parents.[3]

Symptoms

ADHD is characterized by developmentally inappropriate symptoms of inattention, distractibility, hyperactivity, emotional lability, and impulsivity (Table 2).[4]

Table 2. Characteristic ADHD Symptoms[8]

Inattention	Hyperactivity	Impulsivity
Messy work	Fidgetiness or squirming	Impatience
Careless mistakes	Excessive running	Interrupting
Lack of follow-through	Excessive talking	Intrusiveness
Poor listening	Hand tapping	Grabbing objects
Easily distracted	Excessive foot/ leg shaking	Clowning around
Forgetful	Restlessness	Accidents

Diagnosis

ADHD is the most commonly diagnosed behavioral disorder of childhood.[4] The diagnosis of this disorder remains dependent on the reports of observed behaviors from those most closely supervising children, such as parents and teachers.

Interestingly, recorded prevalence rates for ADHD vary substantially, in part, owing to changing diagnostic criteria,[9] different methods of obtaining data, choice of informant (often there are significant discrepancies between parent and teacher ratings),[9] the existence of other medical conditions with similar symptoms, and the inherent subjectivity of the diagnostic criteria.[10]

To minimize these factors, a clinical practice guideline for the diagnosis and evaluation of children with ADHD was recently developed by the American Academy of Pediatrics. Among the guideline recommendations are 1) evaluation by a physician, 2) use of diagnostic criteria from the *DSM-IV*, 3) obtainment of direct evidence of symptoms from parents and classroom teachers, and 4) assessment for coexisting conditions that may make the diagnosis more difficult or complicate treatment planning.[9]

Diagnostic Criteria. The criteria for what constitutes ADHD have broadened, and it is now clear that ADHD may persist into adolescence and adulthood. As a result, more children—especially girls—adolescents, and adults are being diagnosed and treated, and children are often treated for longer periods of time.[11] While the increase in the number of diagnosed children and the concurrent increase in the use of stimulants are cause for concern, experts have concluded that misdiagnosis, overdiagnosis, and overprescription of stimulants for ADHD are not widespread. One report has estimated, based on prescribing rates, that of the 4 million children in the United States with ADHD, only 650,000 (or 1 in 6) are being actively treated, and many of these children may be inadequately or inconsistently treated. A smaller sampling of communities found that only 1 in 8 children with ADHD, within a given year, was actually being treated with ADHD medications. Thus, contrary to public opinion, the data suggest that the majority of children with ADHD are not recognized, evaluated, or adequately treated. This low rate of treatment may, in part, be due to lingering stigma and parental concerns about the use of psychostimulants.[12]

The *DSM-IV* criteria, which reflect the current consensus among clinicians, are based on clinical experience and have more support in the literature than other available diagnostic criteria. When applied appropriately, use of these specific criteria will help ensure an accurate diagnosis and decrease the variation in how the diagnosis is made.[9]

To meet the *DSM-IV* diagnostic criteria for ADHD, the disorder must demonstrate the following:

- Presence for at least 6 months;
- Significant impairment in social, academic, or occupational functioning;
- Evidence in at least 2 settings (eg, home, school, or work);
- Occurrence before the age of 7 years.[8]

There are 3 subtypes of ADHD: 1) predominantly inattentive type; 2) predominantly hyperactive type; and 3) combined type (Table 3).

Table 3. Subtypes of ADHD

Inattentive Type ***At least 6 of the following symptoms must have persisted for at least 6 months.***
Lack of attention to details/ careless mistakes Avoidance of tasks requiring sustained mental effort
Lack of sustained attention Frequent loss of things
Poor listening Easily distractible
Failure to follow through on tasks Forgetful
Poor organization
Hyperactive Type ***At least 6 of the following symptoms must have persisted for at least 6 months.***
Fidgeting/squirming; inappropriately leaving seat Excessive talking
Inappropriately running/climbing Blurting answers
Difficulty with quiet activities Unable to wait turn
Excessively "on the go" Intrusive
Combined Type ***Requires both inattentive and hyperactive criteria be met.***

Incidence and Prevalence

ADHD affects approximately 4%-12% of school-aged children in the United States,[9] appears 3-5 times more often in boys than in girls, and is most common in first-born boys.[3] Reports on the incidence of ADHD in the United States have varied from 2%-20% of grade school-aged children,[3] prompting public concern that the disorder is overdiagnosed or misdiagnosed. Prevalence rates also vary greatly between different geographic regions and across countries.[9] Reports on the prevalence of treatment for ADHD vary by study and by region. One study found that 88% of physician-diagnosed children with ADHD were prescribed methylphenidate, and a survey of Baltimore schools found that 6% of school-aged children received methylphenidate treatment. A Tennessee study, however, found that only 15%-40% of the children diagnosed with ADHD by researchers had been so diagnosed with ADHD by clinicians, and only 21%-32% were receiving drug therapy.[11]

Treatment Options

It has been determined that the response rate for any single stimulant drug in ADHD is approximately 70%, and that up to 90% of children will respond to at least 1 stimulant without major adverse events if drug titration is done carefully.[11] Thus, it appears that this common childhood disorder may be successfully managed in most cases if appropriate stimulant medication is available.

Several studies have demonstrated that children who receive adequate treatment for ADHD have fewer problems with school, peers, and substance abuse and show improved overall function compared with those who do not receive treatment.[13] A wide variety of treatments have been used to treat ADHD. These include psychotropic medications, psychosocial treatment, dietary management, herbal and homeopathic treatments, biofeedback, meditation, and perceptual stimulation/training. Of these, stimulant medications and psychosocial interventions have been most studied.[4]

Psychosocial Treatments. Behavioral strategies such as contingency management (eg, point/token reward systems, timeout, response cost), parent training (parent is taught child management skills), and clinical behavior therapy (parent, teacher, or both are taught to use contingency management procedures) have been demonstrated to produce beneficial effects in short-term studies. Cognitive-behavioral treatment (eg, self-monitoring, verbal self-instruction, self-reinforcement), in contrast, has not been found to be beneficial.[4]

Medication Management. Numerous short-term trials have clearly demonstrated that stimulants are superior to placebo in the reduction of hyperactivity.[14] Methylphenidate is the most studied and most often used of the stimulants.[4]

Given public concerns regarding the use of stimulants in children, wide variances in treatment practices, and the paucity of long-term studies, a 14-month clinical trial of 579 children with ADHD was performed to determine how long-term medication treatment compares with behavioral treatment and if combination treatment (medical and behavioral) has additional benefits.[15]

All groups (medical treatment, behavioral treatment, and combined) showed reductions in ADHD symptoms over time. Primarily, the study found that medication management was superior to behavioral treatment for treating core ADHD symptoms. This was assessed by parents' and teachers' ratings of inattention and teachers' ratings of hyperactivity-impulsivity. Perhaps, surprisingly, combined treatment did not yield significantly greater benefits than medication alone for core ADHD symptoms, although modest advantages for non-ADHD symptom and positive function outcomes were noted. As expected, combined treatment was superior to behavioral treatment alone for the reduction of numerous ADHD symptoms (Table 4).[15]

Table 4. Comparison of Medical Management (MM), Behavioral Management (BM), and Combined Management (CM) for the Treatment of ADHD Symptoms

Measure and Rater	MM vs BM	*P*	CM vs BM	*P*
Inattention				
Teacher	MM > BM	.001	CM > BM	.005
Parent	MM > BM	.001	CM > BM	.001
Hyperactive/ Impulsive				
Teacher	MM ≈ BM	.004*	CM ≈ BM	.04*
Parent	MM > BM	.001	CM > BM	.001

**P* values not significant after Bonferroni correction.
Adapted from MTA Cooperative Group.[15]

Misuse of Stimulants

It is estimated that stimulants are used between 10 and 30 times more frequently in the United States than in the United Kingdom.[14] Given the widespread use of stimulants for the treatment of ADHD, concern has arisen over the potential for abuse in schools. A recent government study reported that actual incidents of stimulant abuse are rare. For the first 7-9 months of the 2000-2001 school year, approximately 8% of public middle and high school principals reported that attention disorder drugs had been diverted or abused at their schools. In most of these cases, principals reported knowledge of only 1 incident. This low prevalence of abuse, in part, may be due to careful practices in schools. Thirty-seven states and the District of Columbia have statutes, regulations, or mandatory policies addressing the administration of medication to students. Such state provisions require schools to

obtain written parental authorization to administer medication, to ensure that the medication is securely stored, and that prescription medication is stored in the original pharmacy container. In the majority of schools, ADHD medications are administered to students by school officials, in most schools (60%) by a nurse. Also, in 96% of schools, medications are kept locked, and students are observed while taking their medications.[16]

Cost of Attention Deficit Hyperactivity Disorder

The resulting academic and social difficulties of children with ADHD have far-reaching and long-term consequences on individuals, families, schools, and society.[4]

Individuals. Children with ADHD often exhibit agitated behavior and an inability to focus on tasks, which may result in dramatic and long-term adverse effects on academic performance, vocational success, and social-emotional development. These children experience low self-esteem, peer rejection, and impairments in learning, social, and family interactions. In addition, they have higher injury rates[17] and are more likely to drop out of high school,[13] abuse drugs, and exhibit antisocial behavior later in life.[17] Approximately 70% of children diagnosed with ADHD will continue to exhibit symptoms of ADHD in adulthood.[13]

Studies have reported that children with ADHD incur significantly higher medical costs than children without ADHD.[18] A study conducted in Rochester, Minnesota, reported that the median costs of medical care over 9 years were more than double for children with ADHD compared with those without ADHD ($4306 versus $1944). The dramatic difference in cost was observed for both males and females and across all age groups[17] (Table 5).

Families and Society. Families with children with ADHD experience increased levels of parental frustration, marital discord, and divorce.[4] On a larger scale, ADHD contributes to societal problems such as violent crime and teenage pregnancy.[4] In addition to the direct costs of medical care for children with ADHD, the cost of ADHD to society is also large. For example, additional national public school expenditures on behalf of students with ADHD may have exceeded $3 billion in 1995.[4] Much of this additional expense stems from special educational programs, which 50%-80% of ADHD children eventually receive.[13]

Table 5. Associated Costs in Children

Medical Treatment	Children With ADHD	Children Without ADHD	Relative Increase
Outpatient mental health visits/year	1.35	.14	9.9
Pharmacy fills/year	11.25	3.30	3.4
Primary care visits/year	3.84	2.36	1.6

Adapted from Guevara et al.[18]

Summary

ADHD is a commonly diagnosed behavioral disorder of childhood that represents a costly major public health problem with profound impact on individuals, families, schools and society. Focalin—an advance in single-isomer chemistry—offers significant improvements for those who suffer with the disorder, particularly with respect to academic performance and behavior. This monograph provides a broad overview of the data pertinent to Focalin: chemistry, nonclinical pharmacology, pharmacokinetics, efficacy, safety, and references.

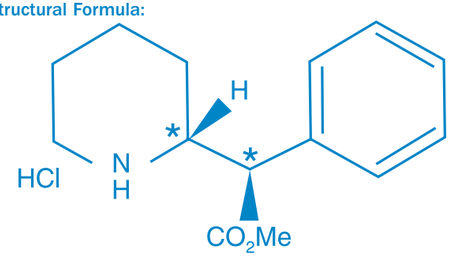
Chemistry

Description

The active ingredient of Focalin is *d-threo*-methylphenidate hydrochloride, which is the single *d* enantiomer of *dl-threo*-methylphenidate hydrochloride. The active component Focalin (Figure 1) has the following characteristics[2]:

Figure 1. Characteristics

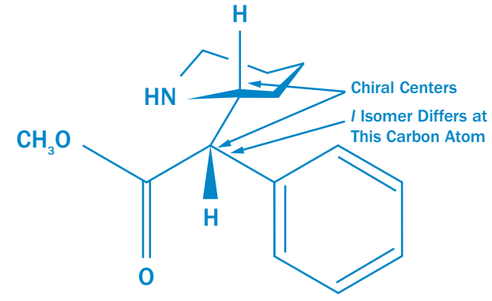
Structural Formula:



Empirical Formula:	$C_{14}H_{19}NO_2 \cdot HCl$
Molecular Weight:	**269.77**
Appearance:	**Focalin is a white to off-white powder**

Focalin is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone, and it contains the following inert ingredients: pregelatinized starch, lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, magnesium stearate, and FD&C Blue No. 1 #5516 aluminum lake (2.5-mg tablets), D&C Yellow Lake #10 (5-mg tablets); the 10-mg tablet contains no dye.[1]

Figure 2. Structure of the Enantiomer *d-threo*-MPH [(2R:2'R)-(+) *threo*-MPH][1]



Stereochemistry of Methylphenidate

Methylphenidate [methyl-phenyl-2-(2'-piperidyl) acetate, or methylphenidate], commonly referred to by the trade name Ritalin, is a 50/50 racemic mixture of *d-threo-* and *l-threo*-methylphenidate.

While current preparations of Ritalin contain a racemic mixture of the *d-threo* and *l-threo* isomers of methylphenidate, studies show that *d-threo*-methylphenidate is the pharmacologically active enantiomer.[5,19] Recent advances in stereospecific manufacturing allow commercial preparations of optically pure *d-threo*-methylphenidate, and a preparation containing only this enantiomer could provide a better therapeutic index than a racemic mixture (Figure 2). Enantioselective behavioral pharmacology with psychostimulants is not uncommon. For example, the *d* isomer of amphetamine (dextroamphetamine) is 3-4 times as potent as the *l* isomer in eliciting CNS excitatory effects.[20]

Nonclinical Pharmacology

Animal Studies

Animal studies have demonstrated stereoselective binding in the brain. In rats injected intravenously with racemic methylphenidate, *d-threo*-methylphenidate was bound specifically to the dopamine reuptake site in the striatum even though both enantiomers were distributed extensively to the entire brain region.[21-23]

Mechanism of Action

It is believed that ADHD sufferers have decreased function of dopamine circuits and are therefore easily distracted. Ritalin helps normalize these levels, allowing ADHD sufferers to focus and pay attention.[24] The pharmacologic actions of Focalin most likely are due to its ability to increase dopamine levels in the striatum region of the brain.[23]

Clinical Pharmacology

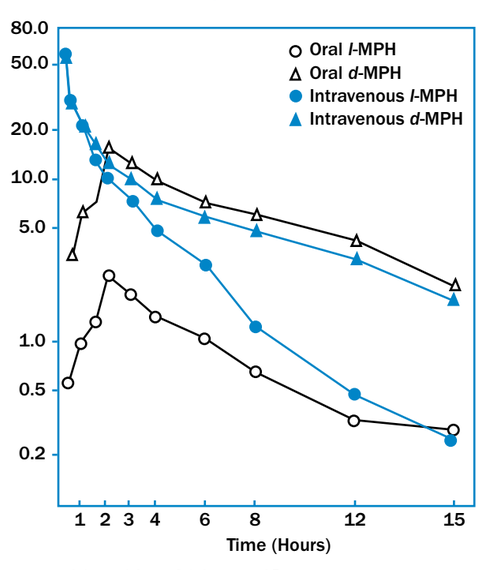
Pharmacokinetics

Absorption. Dexmethylphenidate hydrochloride is readily and completely absorbed following oral administration of Focalin. In patients with ADHD, plasma dexmethylphenidate concentrations increase rapidly, reaching a maximum at about 1-1.5 hours postdose. No differences in the pharmacokinetics of Focalin were noted following single and repeated twice-daily dosing, indicating no significant drug accumulation. Pharmacokinetic profiles of *d-threo*-methylphenidate are similar when equimolar doses of *d-threo*-methylphenidate and *dl-threo*-methylphenidate are administered.[2]

Based on comparison of area under the plasma concentration-time curve following intravenous (10 mg) and oral (40 mg) administration of *dl*-methylphenidate, absolute bioavailability of *d*-methylphenidate is approximately 20% (Figure 3).[2]

Figure 3. Plasma Profile of *d*-MPH and *l*-MPH Following Intravenous Injection of *dl*-MPH 10 mg or Oral Administration of *dl*-MPH 40 mg

Mean plasma concentration versus time plots for Focalin (triangles) and *l*-MPH (circles) after the administration of intravenous MPH (filled symbols) or oral MPH (open symbols).



Adapted from Srinivas et al.[7]

As demonstrated in the Srinivas study, Focalin is distributed very rapidly into the brain after oral administration of *dl*-methylphenidate.[7]

Distribution. Plasma Focalin concentrations in children decline exponentially following oral administration of Focalin. PET scanning studies indicate that Focalin is rapidly and selectively distributed to the striatum (Figure 4). The mean plasma half-life is approximately 2.2 hours. Protein binding has not been determined for Focalin. However, racemic methylphenidate is minimally protein bound (< 20%).[1] *d-threo*-Methylphenidate is distributed specifically to the basal ganglia, while *dl-threo*-methylphenidate contributes only to nonspecific binding. Data in 2 human subjects suggest rapid and selective distribution of Focalin to the striatum (Figure 4).[23]

Metabolism and Excretion. In humans, dexmethylphenidate is metabolized primarily to *d*-α-phenyl-2-piperidine acetic acid (more commonly known as *d*-ritalinic acid, *d*-RA) by de-esterification. This metabolite has little or no pharmacologic activity. There is little or no in vivo interconversion to the *l-threo* enantiomer.

After oral dosing of radiolabeled racemic methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was ritalinic acid, accountable for approximately 80% of the dose (Figure 5).[1]

Food Effect. There is no effect of food on Focalin C_{max} or AUC. The presence of food does, however, reduce the rate of Focalin availability, as evidenced by the increase in time to peak plasma concentration (T_{max}) by about 1.5 hours. Results for *d*-RA are similar; that is, there is a delay in the time of the peak concentration but no differences in C_{max} or AUC. Although the study was conducted in healthy adult volunteers, the results are also applicable to children (Figure 6).[2]

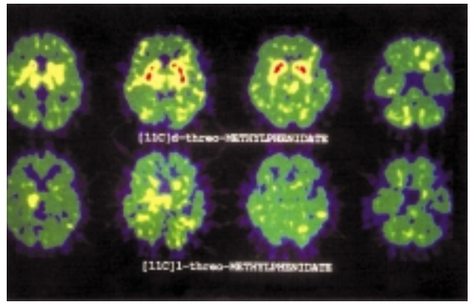
Pharmacodynamics

Dexmethylphenidate HCl is a CNS stimulant. Dexmethylphenidate HCl, the more pharmacologically active enantiomer of the *d* and *l* enantiomers, blocks the reuptake of norephinephrine and dopamine into the presynaptic neuron and increases the release of these monoamines into the extraneuronal space. The mode of therapeutic action in ADHD is not known.[1]

Dose Response and Duration of Effect. In a single-dose crossover study (study 97-M-01), both *dl*-methylphenidate and *d*-methylphenidate demonstrated a significant dose response effect for the control of signs and symptoms of ADHD using an objective instrument, the Math Test, and subjective instruments, the CLAM and Conners Rating Scales. The significant dose response was evident for the Math Test by 1-hour postdose, continuing through the 4-hour test, and decreasing (Focalin) or disappearing (*dl*-methylphenidate) by the 6-hour test significant dose. The significant dose response was evident for the CLAM and Conners scales for all postdose assessments at 2, 3.5, and 6 hours postdose.

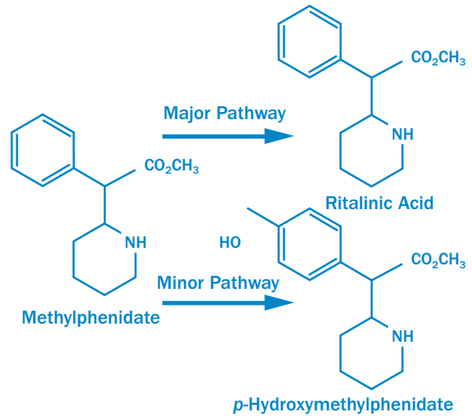
Figure 4. Transaxial PET Images of the Human Brain After Injection of [^{11}C] *d-threo*-MPH and [^{11}C] *l-threo*-MPH

Data in 2 human subjects suggest rapid and selective distribution of Focalin to the striatum.



Adapted from Ding et al.[23]

Figure 5. Metabolic Pathways of *dl*-MPH



Adapted from Patrick et al.[5]

Figure 6. Focalin Food Effect

Approximately 1.5-hour shift in T_{max}; negligible decrease in C_{max}; no change in AUC.

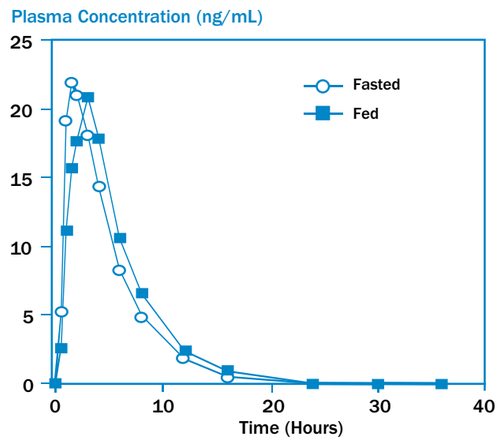
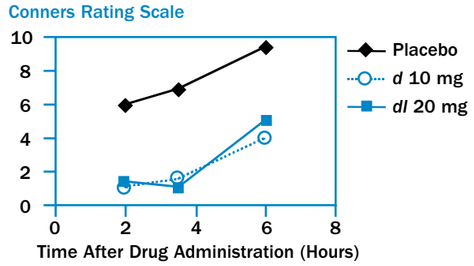
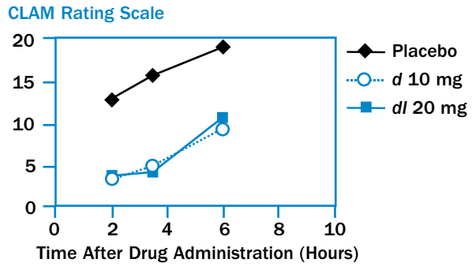
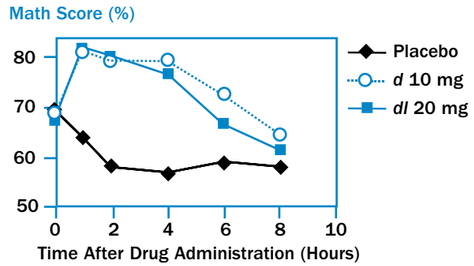


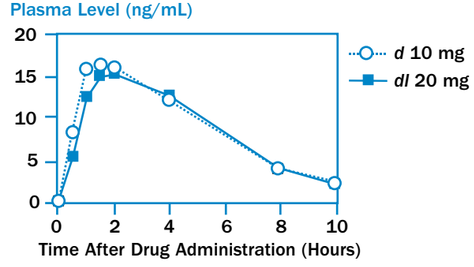
Figure 7. Relationship of Blood Levels to Each Efficacy Variable for High Doses of Study Drug (10 mg Focalin and 20 mg *dl*-MPH): Study 97-M-01

To evaluate the pharmacokinetic/pharmacodynamic relationships of Focalin and *dl*-MPH, graphic comparisons of the plasma levels for Focalin and *dl*-MPH to each efficacy variable are presented for the high doses and placebo.









When compared with placebo, however, there were differences between the 2 study drugs when they were given in doses equimolar for Focalin. At 6 hours, the highest dose of Focalin resulted in a mean Math Test score that was statistically superior to placebo; this difference was not seen after treatment with the highest dose of *dl*-methylphenidate. Similar results indicating that Focalin might have a longer duration of effect were obtained using the behavioral scales. With the CLAM scales, while the highest dose of Focalin and *dl*-methylphenidate produced scores superior to placebo at 6 hours postdose, Focalin was superior to placebo whereas *dl*-methylphenidate was not for the middle and low doses. These observations are not attributed to pharmacokinetic differences because the plasma concentration curves were virtually superimposable (Figure 7).[2]

Clinical Efficacy

Focalin was evaluated in 2 double-blind, parallel-group, placebo-controlled trials in untreated or previously treated patients 6 to 17 years old with a *DSM-IV* diagnosis of ADHD. Both studies included all 3 subtypes of ADHD—combined type, predominantly inattentive type, or predominantly hyperactive-impulsive type. While both children and adolescents were included, the sample was predominantly children; thus, the findings are most pertinent to this age group. In both studies, the primary comparison of interest was Focalin versus placebo.

Focalin (5, 10, or 20 mg/day total dose), *dl-threo*-methylphenidate HCl (10, 20, or 40 mg/day total dose), and placebo were compared in a multicenter, 4-week, parallel group study in 132 patients. Patients took the study medication twice daily, 3.5 to 5.5 hours between doses. Treatment was initiated with the lowest dose, and doses could be doubled at weekly intervals, depending on clinical response and tolerability, up to the maximum dose. The change from baseline to week 4 of the averaged score (an average of 2 ratings during the week) of the Teacher SNAP-ADHD Rating Scale, a scale for assessing ADHD symptoms, was the primary outcome. Patients treated with Focalin showed a statistically significant improvement in symptom scores from baseline over patients who received placebo.

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

Table 6. Overview of Efficacy Procedures in the Double-Blind Studies[2]

Study 97-M-02	1-Week Single-Blind Placebo (Visits-3)	4-Week Double-Blind Treatment				
		Baseline (Visit 3)	Week 1 (Visit 4)	Week 2 (Visit 5)	Week 3 (Visit 6)	Week 4 (Visit 7)
Study 97-M-03	6-Week Open-Label Focalin (Visits 2-8)	2-Week Double-Blind Withdrawal				
		Baseline (Visit 8)	Week 1 (Visit 9)	Week 2 (Visit 10)		
Study Procedure						
Teacher SNAP-ADHD		■*	■*	■*	■*	■*
Parent SNAP-ADHD		■†	■†	■†	■†	■†
CGI-I		■‡	■	■	■	■
CGI-S	■	■‡				
Math Test (Home)		■†	■	■	■	■
Math Test (Clinic)		■‡	■	■	■	■
Study Medication	■	■	■	■	■	
Study Termination						■

*To be recorded twice weekly by the teacher at school in the afternoon, during the week preceding the listed clinic visit.
† SNAP-ADHD to be recorded twice daily on the weekends by the parent and any day the child was not in school, and the Math Test once daily during the week preceding the clinic visit.
‡ To be evaluated prior to dispensing double-blind medication.

Efficacy Parameters

The primary measure of efficacy for study 97-M-02 was the Teacher Swanson, Nolan, and Pelham ADHD Scale (SNAP-ADHD), an 18-item scale worded to mirror the *DSM-IV* symptoms and scored from 0-3 with higher scores indicating greater severity. Secondary efficacy parameters included the Parent SNAP, CGI-I, Clinical Global Impressions-Severity (CGI-S), percent of therapeutic responders, and Math Test scores (Table 6).[2]

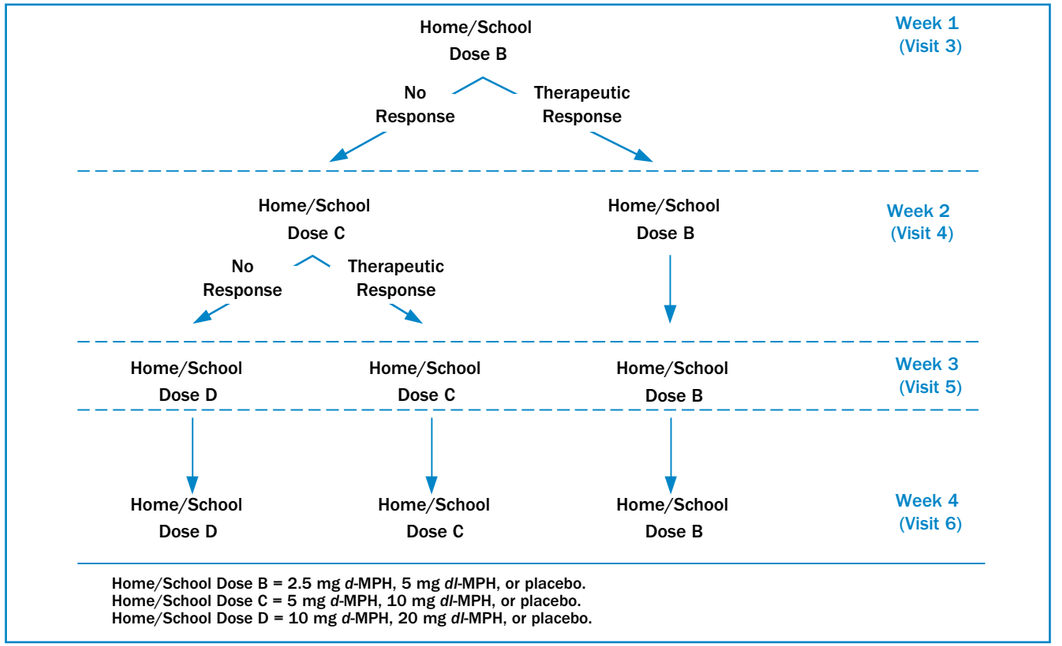
Efficacy Results

Study 97-M-02. Study 97-M-02 was designed 1) to determine the comparative efficacy of twice-daily doses of Focalin versus placebo in reducing symptoms of ADHD in children, and 2) to determine the comparative safety of Focalin and placebo, given twice daily, in children with ADHD. The secondary objective of this study was to compare the duration of action of Focalin versus placebo to the duration of *dl*-methylphenidate versus placebo.

This double-blind, randomized, placebo-controlled study was preceded by a 1-week, single-blind, placebo, lead-in phase. All children received placebo in the single-blind phase, designed to familiarize teachers and parents with the use of the SNAP-ADHD Rating Scales and disqualify children who demonstrated a therapeutic response to placebo. A therapeutic response was based on the investigator's overall assessment using the CGI-I. During the 4-week, double-blind phase, children were randomized to Focalin, *dl*-methylphenidate, or placebo. After weeks 1 and 2 of the double-blind period, dose escalation was permitted, based on therapeutic response (Figure 8). One hundred thirty-three (133) children entered the single-blind lead-in; 132 children were randomized to double-blind treatment (44 to Focalin, 46 to *dl*-methylphenidate, and 42 to placebo).[2]

Figure 8. Schematic of Dose Administration During Double-Blind Phase[2]

The double-blind phase was preceded by a 1-week, single-blind, placebo (dose A), lead-in phase. The initial dose of Focalin was 2.5 mg, twice daily, while the initial dose of *dl*-methylphenidate was 5 mg, twice daily. The maximum dose of Focalin given was 10 mg, twice daily, while the maximum dose of *dl*-methylphenidate was 20 mg, twice daily. Note: dose A = placebo.



Home/School Dose B = 2.5 mg *d*-MPH, 5 mg *dl*-MPH, or placebo.
Home/School Dose C = 5 mg *d*-MPH, 10 mg *dl*-MPH, or placebo.
Home/School Dose D = 10 mg *d*-MPH, 20 mg *dl*-MPH, or placebo.

Table 7. Weekly Teacher SNAP-ADHD Results – Observed Cases[2]*

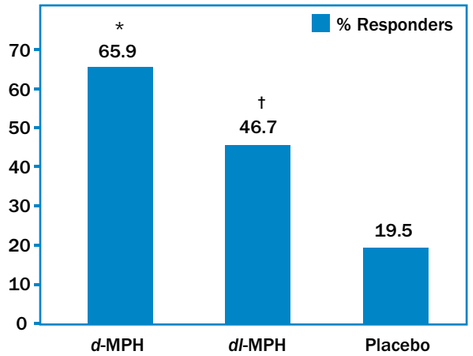
Improvement from baseline for the Focalin and *dl*-MPH treatment groups was equivalent to 1 standard deviation (SD) at baseline and reflects strong clinical improvement compared with placebo, with a smaller change (–0.2) indicating a lack of improvement in this group.

Average Test Score		*d*-MPH n = 44	*dl*-MPH n = 46	Placebo n = 42
Baseline:	n	42	41	41
	Mean ± SD	1.4 ± 0.7	1.8 ± 0.7	1.6 ± 0.7
	Range	0.1–2.9	0.4–2.9	0.1–2.8
Week 1:	n	42	41	39
	Mean ± SD	1.1 ± .7	1.4 ± 0.8	1.7 ± 0.7
	Range	0.1–2.7	0.3–2.9	0.3–3.0
Week 2:	n	40	40	37
	Mean ± SD	0.9 ± 0.6	1.3 ± 0.8	1.5 ± 0.8
	Range	0.1–2.6	0.2–2.9	0.3–3.0
Week 3:	n	38	39	37
	Mean ± SD	0.8 ± 0.6	1.2 ± 0.8	1.5 ± 0.8
	Range	0.0–2.1	0.0–2.9	0.0–3.0
Week 4:	n	39	37	36
	Mean ± SD	0.8 ± 0.7	0.9 ± 0.8	1.4 ± 0.8
	Range	0.0–3.0	0.1–2.9	0.1–3.0

*The number of patients in each treatment group is smaller than the number of patients enrolled because of patient discontinuation and patients with missing data at specific visits.

Figure 9. CGI-I: Percent of Responders at Visit 7[2]

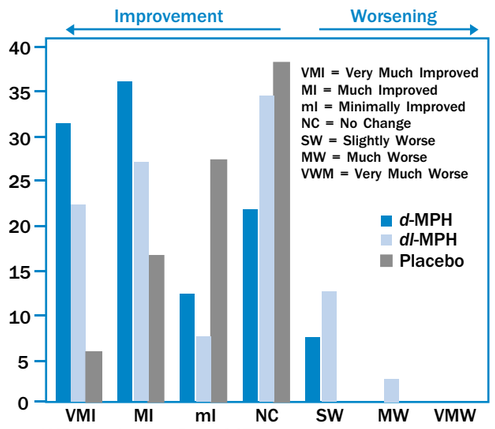
At the end of the double-blind period, approximately two-thirds of the patients randomized to Focalin responded to treatment compared with approximately 20% on placebo. This difference was statistically significant (*P* = .001).



*P < .0001 vs placebo.
†P = .0082 vs placebo.
d-MPH vs *dl*-MPH = NS (P = .0089).

Figure 10. CGI-I: Improvement at Week 4[2]

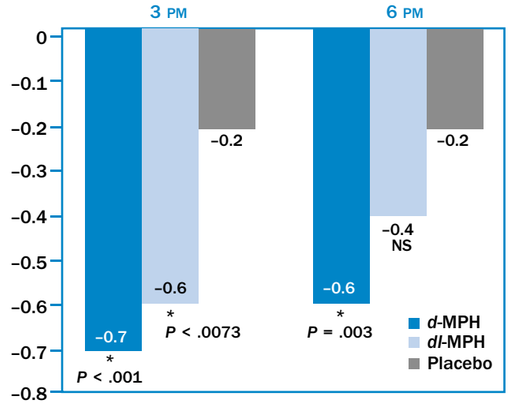
In general, improvements in CGI-I were seen in children randomized to Focalin and *dl*-MPH, whereas less change was seen in children randomized to placebo.



d-MPH vs placebo, P = .0045.
dl-MPH vs placebo, P = .007.
d-MPH vs *dl*-MPH, P = .0539.
Mantel-Haenszel Test across all values.

Figure 11. Parent SNAP-ADHD: Ratings at 3 PM and 6 PM (Change from Baseline at Week 4)[2]

Compared with baseline, both the Focalin and *dl*-MPH groups had statistically significant improvements in the 3 PM Parents SNAP-ADHD scales to the last visit. In contrast, only the Focalin group had a statistically significant reduction from baseline in the SNAP-ADHD score.



*P < .01 vs placebo (LOCF change from baseline).

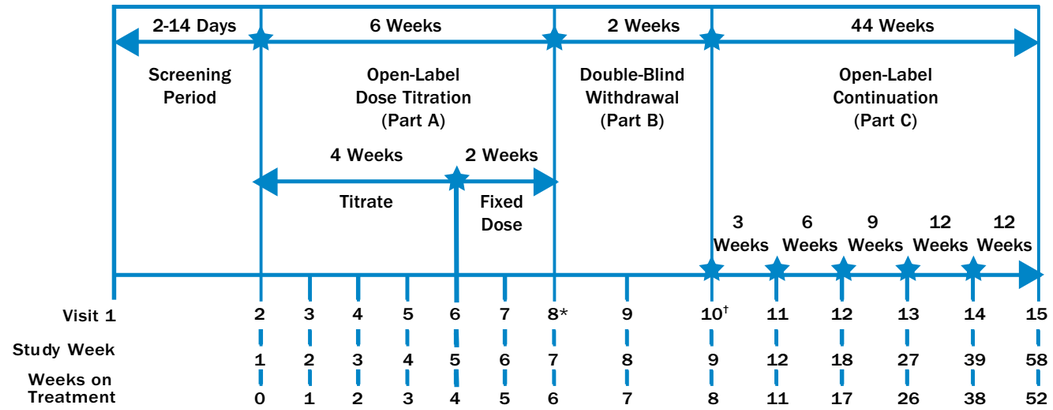
The primary efficacy analysis indicated that the change from baseline of Teacher SNAP-ADHD scores after 4 weeks of double-blind treatment was significantly greater in the Focalin group than in the placebo group (P = .0004) (Table 7).

The results for the primary and secondary measures of efficacy support the effectiveness of Focalin in ameliorating the symptoms of ADHD significantly more than placebo as measured by CGI-I ratings, by 3 PM and 6 PM Parents SNAP-ADHD ratings, and Math Tests administered at home and in the clinic (Figures 9-11).

Study 97-M-03. Study 97-M-03 was designed to determine the comparative efficacy of Focalin given in a dose range of 2.5 to 10 mg b.i.d. relative to placebo in maintaining a reduction of ADHD symptoms in children who demonstrated a response to Focalin. The secondary objectives were to determine the long-term safety (up to 1 year) and the duration of efficacy of Focalin in children with ADHD.

A screening period of up to 14 days was followed by 3 parts: A, B, and C. In part A, a 6-week, open-label, titration phase, all patients received Focalin. During the first 4 weeks, the dosage was titrated once weekly to identify the optimal dosage of Focalin for each patient. During the last 2 weeks of part A, the optimal dose level was maintained. Part B was a double-blind, randomized, placebo-controlled, withdrawal phase lasting 2 weeks. Part C was an open-label treatment phase in which all patients received Focalin for up to 44 weeks (Figure 12). Primary efficacy evaluation was the percent of failures based on the CGI-I scale at the end of part B. Other efficacy variables included the CGI-I, SNAP-ADHD (Teacher and Parent), and the Math Test.[2]

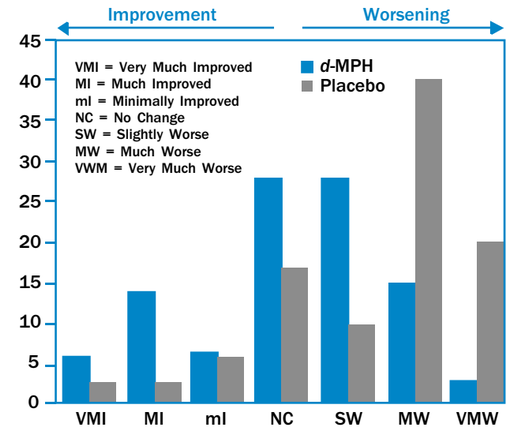
Figure 12. Schematic of Study 97-M-03



Visits were to occur within 0.5 and 3 hours of the child ingesting the study medication. The interval between visit 1 and visit 2 was preferably within 4 to 7 days; however, it could be 2 to 14 days. All other visits were ± 2 days when weekly or bimonthly and ± 4 days when monthly or longer.
*Randomization occurred at the end of visit 8.
†End of part B was visit 10 or visit 9 if patient stopped study after visit 9.

Figure 13. CGI-I: Evaluation 2 Weeks After Randomization[2]

By the end of the 2-week withdrawal, 19 of 35 (54.3%) *d*-MPH–treated patients had a CGI-I score "no change" or "improved," whereas 11 of 39 (28.2%) placebo-treated patients had a CGI-I score "no change" or "improved."



Tx failure = MW or VMW.
17.1% *d*-MPH vs 61.5% placebo were considered treatment failures.
P = .001 for *d*-MPH vs placebo.

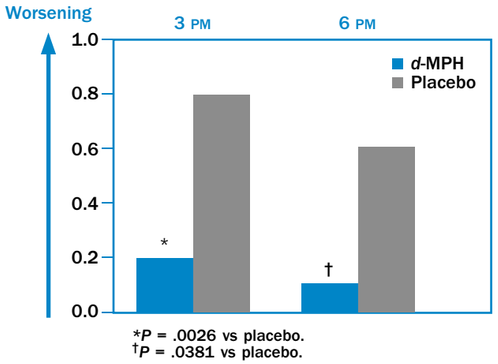
One hundred sixteen patients were screened, and 89 patients were included in the safety sample; the intent to treat sample was 75 patients (35 randomized to Focalin and 40 randomized to placebo).[2]

The results of the primary efficacy analysis (comparison of change from baseline 2 weeks after randomization) indicated that the treatment failure rate in the placebo group (61.5%) was more than 3 times greater than in the group randomized to Focalin (17%); this difference was statistically significant (P = .001) (Figure 13).

Results of secondary measures of efficacy (Teacher and Parent SNAP-ADHD and Math Test scores) were consistent with the results of the primary efficacy analysis (Figures 14-15). The behavioral scores based on the Teacher and/or Parent SNAP-ADHD were consistent with children having no or mild symptoms (score < 1.0) when measured at 3 hours (Teacher/Parent) and 6 hours (Parent) after taking Focalin. Children taking placebo did not display good behavioral control (SNAP-ADHD assessment > 1.0). The Teacher SNAP-ADHD score mean change from visit 8 to visit 10 was statistically significantly worse in the placebo group than in the Focalin group (P = .028), indicating a deterioration of symptoms in the placebo group when compared with the Focalin group. No change in mean score occurred in the Focalin group, which had already achieved maximum and stable benefit during the open-label titration period.

Figure 14. Parent SNAP-ADHD: Change from Baseline

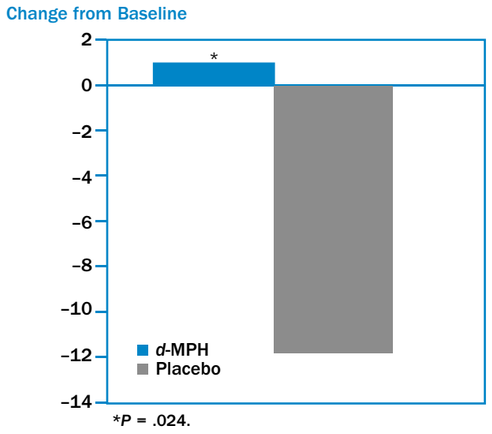
The secondary endpoint of the Parent SNAP-ADHD was superior to placebo at 3 and 6 hours. The small change in score for *d*-MPH from baseline suggests that it is still effective at 3 PM and 6 PM.



*P = .0026 vs placebo.
†P = .0381 vs placebo.

Figure 15. Math Test from Baseline[2]

These data suggest that the improvement in Math Test scores seen at the end of part A (6-week, open-label) of treatment were sustained during part B (double-blind withdrawal) of the study.



*P = .024.

The 3 PM Parent SNAP-ADHD scores at visits 8 and 10 for each treatment were significantly different at P = .0026, demonstrating that the placebo group worsened when compared with the Focalin group. Also, differences between 6 PM Parent SNAP-ADHD scores at visits 8 and 10 were significant (P = .0381). The Math Test scores show a mean increase of 0.9 (median 5.3) in the total number of correct answers for the Focalin group. In the placebo group, patients averaged 11.7 fewer correct answers (median 10.5). The difference between the changes from baseline Math Test scores for the 2 treatment groups was statistically significant (P = .024).

The superior control of ADHD symptoms by Focalin 6 hours after the second daily dose is supported by analysis of the 6 PM Parent SNAP-ADHD measure and the 6 PM Weekend Math Test. Both show a statistically significant difference between the scores for the Focalin group compared with placebo treatment groups.

Safety and Tolerability

Dosing

In both studies, the majority of patients were taking the highest dose of their randomized study medication, including *d*-methylphenidate, *dl*-methylphenidate, or placebo. Even though the designs of the 2 well-controlled studies were different, the approach to dosing was similar. Patients who had not received psychostimulants within the previous 30 days started with the lowest dose of *d*-methylphenidate, 2.5 mg. b.i.d. (in the case of study 97-M-02, this was on a double-blind basis). In patients receiving psychostimulants (*dl*-methylphenidate in the majority of patients), dosing was initiated at an equimolar dose of *d*-methylphenidate (again on a double-blind basis in study 97-M-02). Dosing was to be escalated on the basis of therapeutic response. In study 97-M-02, the double-blind dose was to be held constant during the final 2 weeks. In study 97-M-03, patients were to be titrated to their maximal effective dose. During the 2-week, double-blind withdrawal phase, they were randomly assigned to that dose or placebo for 2 weeks (Table 8).[2]

Safety Results

The results support the overall safety of Focalin when given in doses that range from 2.5 mg b.i.d. to 10 mg b.i.d. The premarketing development program for Focalin included exposures in a total of 696 participants in clinical trials (684 patients, 12 healthy adult subjects).[1] Focalin was well tolerated by patients, and the adverse events were consistent with the known and acceptable adverse reactions in methylphenidate-containing products. No previously unknown adverse events for stimulants were reported. Most symptoms associated with stimulant use are mild, and many resolve after a brief period of time or are easily managed.[2]

Adverse Events Associated with Discontinuation of Treatment. No Focalin-treated patients in placebo-controlled studies (97-M-02 or 97-M-03) discontinued owing to adverse events. Overall, 50 of 684 children treated with Focalin discontinued because of adverse events (Table 9).[1]

Adverse Events Occurring at an Incidence of 1% or More Among Focalin-Treated Patients. The incidence of treatment-emergent adverse events that occurred in 2 or more of the patients in any 1 treatment group is summarized in Table 10.

Table 8. Numbers of Patients by Dose of Study Drug Dispensed[2]

Treatment Group	Actual Dose*	Study 97-M-02 (Final Week)	Study 97-M-03 Baseline (Visit 8)†	Study 97-M-03 Week 1 (Visit 9)
Last Observation Carried Forward (LOCF)				
d-Methylphenidate (n = 44)	5 mg/day (B)	4 (9.1%)	0 0	
	10 mg/day (C)	5 (11.4%)	10 (29.4%)	11 (31.4%)
	20 mg/day (D)	35 (79.5%)	24 (70.6%)	24 (68.6%)
dl-Methylphenidate (n = 46)	10 mg/day (B)	8 (17.4%)		
	20 mg/day (C)	8 (17.4%)		
	40 mg/day (D)	30 (65.2%)		
Placebo (n = 42)	B	2 (4.8%)	1 (2.5%)	1 (2.6%)
	C	2 (4.8%)	7 (17.5%)	7 (17.9%)
	D	38 (90.5%)	32 (80.0%)	31 (79.5%)

Source: Clinical Study Report 97-M-02, Table 12.0; dosing by visit is summarized in Table 12.1 and separated as naïve and nonnaïve patients in Tables 12.1.1 and 12.1.2; Clinical Study Report 97-M-03 Table 12.1.

* The double blind was maintained by labeling drug supplies as "B" (corresponding to 2.5 mg *d*-MPH, 5 mg *dl*-MPH, or matching placebo tablets), "C" (corresponding to 5 mg *d*-MPH, 10 mg *dl*-MPH, or matching placebo tablets), and "D" (corresponding to 10 mg *d*-MPH, 20 mg *dl*-MPH, or matching placebo tablets).

† Represents the end of 6 weeks of open-label *d*-MPH treatment.

Table 9. Controlled Studies: Discontinuation for Any Reason[1]

Discontinuation	Overall *d*-MPH	Clinical Pharmacology	Placebo-Controlled Studies *d*-MPH	Placebo-Controlled Studies *dl*-MPH	Placebo-Controlled Studies Placebo
Exposed	**689**	**43**	**79**	**46**	**82**
Completed	**454 (65.9%)**	**42 (97.7%)**	**76 (96.2%)**	**40 (87.0%)**	**76 (92.7%)**
Discontinued		**1 (2.3%)**	**3 (3.8%)**	**6 (13.0%)**	**6 (7.3%)**
Reason for Discontinuation					
Adverse event	50 (7.3%)	0	0	1 (2.2%)	2 (2.4%)
Lack of efficacy	62 (9.0%)	0	0	0	3 (3.7%)
Withdrawn consent	10 (1.5%)	1 (2.3%)	0	0	0
Protocol violation	52 (7.5%)	0	3 (3.8%)	1 (2.2%)	2 (2.4%)
Lost to follow-up	44 (6.4%)	0	0	3 (6.5%)	0
Other	12 (1.7%)	0	0	1 (2.2%)	0

Note: There were a total of 105 patients who rolled over from study 97-M-02 to study 97-M-03, including 38 patients who received Focalin in both studies. Five patients participated in 2 studies and are double counted; therefore, total unique exposure is 684 patients.

Table 10. Treatment-Emergent Adverse Events Occurring in 2 or More Patients in Any One Treatment Group During Double-Blind Treatment in Studies 97-M-02 and 97-M-03[2]

Body System/Adverse Event (COSTART)	Number of Unique Patients (%)		
	d-Methylphenidate (n = 79)	*dl*-Methylphenidate (n = 46)	Placebo (n = 82)
Body as a Whole	**28 (35.4%)**	**20 (43.5%)**	**27 (32.9%)**
Abdominal pain	12 (15.2%)	2 (4.3%)	5 (6.1%)
Accidental injury	4 (5.1%)	4 (8.7%)	5 (6.1%)
Chest pain	2 (2.5%)	0 0	
Fever	4 (5.1%)	3 (6.5%)	1 (1.2%)
Flu syndrome	2 (2.5%)	0	3 (3.7%)
Headache	10 (12.7%)	11 (23.9%)	7 (8.5%)
Pain	4 (5.1%)	1 (2.2%)	3 (3.7%)
Viral infection	2 (2.5%)	4 (8.7%)	5 (6.1%)
Digestive System	**19 (24.1%)**	**10 (21.7%)**	**7 (8.5%)**
Anorexia	5 (6.3%)	5 (10.9%)	1 (1.2%)
Diarrhea	3 (3.8%)	1 (2.2%)	1 (1.2%)
Gastroenteritis	0 0	2 (2.4%)	
Nausea	7 (8.9%)	6 (13.0%)	1 (1.2%)
Vomiting	4 (5.1%)	3 (6.5%)	3 (3.7%)
Metabolic and Nutritional System	**3 (3.8%)**	**1 (2.2%)**	**0**
Ketosis*	2 (2.5%)	0	0
Musculoskeletal System	**0**	**1 (2.2%)**	**2 (2.4%)**
Myalgia	0	1 (2.2%)	2 (2.4%)
Nervous System	**11 (13.9%)**	**12 (26.1%)**	**7 (8.5%)**
Emotional lability	3 (3.8%)	2 (4.3%)	1 (1.2%)
Insomnia	2 (2.5%)	2 (4.3%)	3 (3.7%)
Nervousness	2 (2.5%)	1 (2.2%)	1 (1.2%)
Personality disorder	2 (2.5%)	1 (2.2%)	0
Somnolence	3 (3.8%)	2 (4.3%)	2 (2.4%)
Respiratory System	**15 (19.0%)**	**8 (17.4%)**	**11 (13.4%)**
Cough increased	2 (2.5%)	2 (4.3%)	1 (1.2%)
Epistaxis	3 (3.8%)	1 (2.2%)	1 (1.2%)
Pharyngitis	2 (2.5%)	2 (4.3%)	2 (2.4%)
Rhinitis	8 (10.1%)	2 (4.3%)	6 (7.3%)
Skin and Appendages	**3 (3.8%)**	**2 (4.3%)**	**5 (6.1%)**
Eczema	2 (2.5%)	0	0
Herpes simplex	0	0	2 (2.4%)
Special Senses	**2 (2.5%)**	**1 (2.2%)**	**2 (2.4%)**
Ear pain	0	0	2 (2.4%)

*This actually reflects ketones in the urine.

Laboratory Tests

Clinical laboratory tests included serum biochemistry parameters, complete blood count with differential and platelet count, and urinalysis. The laboratory measures were analyzed by mean change from baseline and identification of clinically significant abnormalities.[2]

Methylphenidate has been associated with small increases in blood pressure and pulse. This is also true for Focalin. Mean changes are small (< 5 mm Hg increase in blood pressure and 5 bpm pulse rate in the double-blind studies). This magnitude of change is not clinically significant. Occasional patients, however, have more significant increases in blood pressure or pulse. These were reported as adverse events in approximately 1% of patients. Consequently, vital sign monitoring is indicated during treatment with Focalin.[2]

There were no clinically significant drug-related changes in laboratory parameters attributable to Focalin. There were occasional reports of elevated liver enzymes, decreased white blood cell or neutrophil counts, increased eosinophils, and anemia. These were reported as adverse events in small numbers of patients (elevated liver enzymes, 1.5%; decreased white blood cell or neutrophil counts, 0.3%; increased eosinophils, 0.9%).[2]

Indications

Focalin is indicated for the treatment of ADHD. The efficacy of Focalin in the treatment of ADHD was established in 2 controlled trials of patients 6 to 17 years of age who met *DSM-IV* criteria for ADHD (see Focalin Prescribing Information, Clinical Studies).

Contraindications

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

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

Glaucoma. Focalin is contraindicated in patients with glaucoma.

Tics. Focalin is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see Focalin Prescribing Information, Adverse Reactions).

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

Warnings

Depression. Focalin should not be used to treat severe depression.

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

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

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

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

Hypertension and Other Cardiovascular Conditions. Focalin should be used cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Focalin, especially those with hypertension.

In the placebo-controlled studies, the mean pulse increase was 2-5 bpm for both Focalin and racemic methylphenidate compared with placebo, with mean increases of systolic and diastolic blood pressure of 2-3 mm Hg, compared with placebo. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, for example, those with preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism.

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

Use in Children Under 6 Years of Age. Focalin should not be used in children under 6 years, as safety and efficacy in this age group have not been established.

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

Precautions

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

Information for Patients. Patient information for Focalin may be found in the full prescribing information in the back of this monograph. To assure safe and effective use of Focalin, the information and instructions provided in the patient information section should be discussed with patients.

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

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

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility. Lifetime carcinogenicity studies have not been carried out with dexmethylphenidate. In a lifetime carcinogenicity study carried out in B6C3F1 mice, racemic methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. Hepatoblastoma is a relatively rare rodent malignant-type tumor. 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 in 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 cells.

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

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

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

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

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

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

Adverse Reactions

The premarketing development program for Focalin included exposures in a total of 696 participants in clinical trials (684 patients, 12 healthy adult subjects). These participants received Focalin 5, 10, or 20 mg/day. The 684 patients with ADHD (aged 6 to 17 years) were evaluated in 2 controlled clinical studies, 2 clinical pharmacology studies, and 2 uncontrolled long-term safety studies. Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, and results of physical examinations, vital sign and body weight measurements, and laboratory analyses.

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

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.[1]

Adverse Findings in Clinical Trials with Focalin

Adverse Events Associated with Discontinuation of Treatment. No Focalin-treated patients discontinued owing to adverse events in 2 placebo-controlled trials. Overall, 50 of 684 children treated with Focalin (7.3%) experienced an adverse event that resulted in discontinuation. The most common reasons for discontinuation were twitching (described as motor or vocal tics), anorexia, insomnia, and tachycardia (approximately 1% each).

Adverse Events Occurring at an Incidence of 5% or More Among Focalin-Treated Patients. Table 11 enumerates treatment-emergent adverse events for 2 placebo-controlled, parallel-group trials in children with ADHD at Focalin doses of 5, 10, and 20 mg/day. The table includes only those events that occurred in 5% or more of patients treated with Focalin where the incidence in patients treated with Focalin was at least twice the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that 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 nondrug factors to the adverse event incidence rate in the population studied.

Table 11. Treatment-Emergent Adverse Events* Occurring During Double-Blind Treatment in Clinical Trials of Focalin

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

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

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

Other reactions include:

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

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

Blood/lymphatic: leukopenia and/or anemia
Hepato-biliary: abnormal liver function, ranging from transaminase elevation to hepatic coma
Psychiatric: transient depressed mood
Skin/subcutaneous: scalp hair loss

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a 10-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, like other methylphenidate products, is classified as a Schedule II Controlled Substance by federal regulation.

Abuse, Dependence, and Tolerance

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

Overdosage

Signs and Symptoms

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

Recommended Treatment

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

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

Poison Control Center

As with the management of all overdosage, the possibility of multiple-drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.[1]

Dosage and Administration

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

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

Patients New to Methylphenidate

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

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

Patients Currently Using Methylphenidate

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

Maintenance/Extended Treatment

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

Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse events occurs, 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.[1]

How Supplied[1]

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

Dose	NDC Code
Tablets 2.5 mg – blue Bottles of 100	NDC 0078-0380-05
Tablets 5 mg – yellow Bottles of 100	NDC 0078-0381-05
Tablets 10 mg – white Bottles of 100	NDC 0078-0382-05

Store at 25°C (77°F); excursions permitted 15°C-30°C (59°F-86°F). (See USP Controlled Room Temperature.) Protect from light and moisture.

Conclusion

Focalin is a new chemically refined form of Ritalin—the most studied and most commonly used stimulant for the treatment of ADHD in children 6 years of age and older. Like Ritalin, Focalin has been proven to be safe and effective in clinical studies, significantly improving attention.

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Focalin™

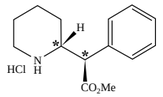
(dexmethylphenidate hydrochloride)
Tablets

Rx only

Prescribing Information

DESCRIPTION

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



Note: * = asymmetric carbon centers

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

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

CLINICAL PHARMACOLOGY

Pharmacodynamics

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

Pharmacokinetics

Absorption

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

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

Food Effects

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

Distribution

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

Metabolism and Excretion

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

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

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

Special Populations

Gender

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

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

Race

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

Age

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

Renal Insufficiency

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

Hepatic Insufficiency

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

Clinical Studies

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

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

Figure 1
Mean Change from Baseline in Teacher SNAP-ADHD Scores in a 4-week Double-Blind Placebo-Controlled Study of Focalin™*

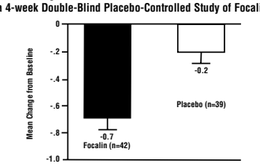
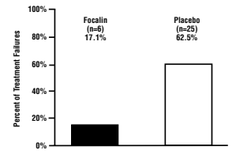


*Figure 1: Error bars represent the standard error of the mean.

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

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



INDICATION AND USAGE

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

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

A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that cause impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning; and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the inattentive type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go," excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

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

Long-term Use

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

CONTRAINDICATIONS

Agitation

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

Hypersensitivity to Methylphenidate

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

Glaucoma

Focalin is contraindicated in patients with glaucoma.

Tics

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

Monoamine Oxidase Inhibitors

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

WARNINGS

Depression

Focalin should not be used to treat severe depression.

Fatigue

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

Long-Term Suppression of Growth

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

Psychosis

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

Seizures

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

Hypertension and Other Cardiovascular Conditions

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Focalin, especially those with hypertension. In the placebo controlled studies, the mean pulse increase was 2-5 bpm for both Focalin and racemic methylphenidate compared to placebo, with mean increases of systolic and diastolic blood pressure of 2-3 mmHg, compared to placebo. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or hyperthyroidism.

Visual Disturbance

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

Use in Children Under 6 Years of Age

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

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

PRECAUTIONS

Hematologic Monitoring

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

Information for Patients

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

Drug Interactions

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

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

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

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

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

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

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

Pregnancy

Pregnancy Category C

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

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

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

Nursing Mothers

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

Pediatric Use

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

ADVERSE REACTIONS

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

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

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

Adverse Findings in Clinical Trials with Focalin

Adverse Events Associated with Discontinuation of Treatment

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

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

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

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

Table 1

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

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

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

Adverse Events with Other Methylphenidate HCl Products

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

Other reactions include:

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

Gastrointestinal: nausea

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

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

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

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

Blood/lymphatic: leukopenia and/or anemia

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

Psychiatric: transient depressed mood

Skin/subcutaneous: scalp hair loss

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

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

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

Abuse, Dependence, and Tolerance

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

OVERDOSAGE

Signs and Symptoms

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

Recommended Treatment

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

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

Poison Control Center

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

DOSAGE AND ADMINISTRATION

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

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

Patients New to Methylphenidate

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

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

Patients Currently Using Methylphenidate

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

Maintenance/Extended Treatment

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

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

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

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

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

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

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

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

[see USP Controlled Room Temperature]

Protect from light and moisture.

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

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

Focalin™
(dexmethylphenidate hydrochloride) CII
Tablets

Rx only

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

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

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

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

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

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

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

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

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

Who Should Not Take Focalin?
You should NOT take Focalin if:

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

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

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

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

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

What Must I Discuss with my Doctor before Taking Focalin?
Talk to your doctor ***before*** taking Focalin if you:

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

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

Can I Take Focalin with Other Medicines?
Tell your doctor about ***all*** medicines that you are taking. Your doctor should decide whether you can take Focalin with other medicines. These include:

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

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

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

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

Other Important Safety Information
Abuse of Focalin can lead to dependence.

Tell your doctor if you have ever abused or been dependent on alcohol or drugs, or if you are now abusing or dependent on alcohol or drugs.

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

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

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

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

What Else Should I Know about Focalin?
Focalin has not been studied in children under 6 years of age.

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

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

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

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

Keep Out of the Reach of Children

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Manufactured for:
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East Hanover, NJ 07936

By:
Mikart, Inc.
Atlanta, GA 30318

Short-Acting

Focalin™ CII

dexmethylphenidate HCl tablets 2.5 mg, 5 mg, 10 mg

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

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