CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078458

LABELING

Rx Only

MEDICATION GUIDE
METHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES (LA)

CII

Read the Medication Guide that comes with methylphenidate hydrochloride extended-release capsules (LA) before you or your child starts taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your or your child's treatment with methylphenidate hydrochloride extended-release capsules (LA).

What is the most important information I should know about Methylphenidate Hydrochloride Extended-Release Capsules (LA)?

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

1. Heart-related problems:

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

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

Your doctor should check you or your child carefully for heart problems before starting methylphenidate hydrochloride extended-release capsules (LA).

Your doctor should check your or your child's blood pressure and heart rate regularly during treatment with methylphenidate hydrochloride extended-release capsules (LA).

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking methylphenidate hydrochloride extended-release capsules (LA).

2. Mental (Psychiatric) problems:

All Patients

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

Children and Teenagers

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

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

Call your doctor right away if you or your child have any new or worsening mental symptoms or problems while taking methylphenidate hydrochloride extended-release capsules (LA), especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

What are Methylphenidate Hydrochloride Extended-Release Capsules (LA)?

Methylphenidate hydrochloride extended-release capsules (LA) are a central nervous system stimulant prescription medicine. **It is used for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD).** Methylphenidate hydrochloride extended-release capsules (LA) may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Methylphenidate hydrochloride extended-release capsules (LA) should be used as a part of a total treatment program for ADHD that may include counseling or other therapies.

Methylphenidate hydrochloride extended-release capsules (LA) are a federally controlled substance (CII) because it can be abused or lead to dependence. Keep methylphenidate hydrochloride extended-release capsules (LA) in a safe place to prevent misuse and abuse. Selling or giving away methylphenidate hydrochloride extended-release capsules (LA) may harm others, and is against the law.

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

Who should not take Methylphenidate Hydrochloride Extended-Release Capsules (LA)?

Methylphenidate hydrochloride extended-release capsules (LA) should not be taken if you or your child:

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

Methylphenidate hydrochloride extended-release capsules (LA) should not be used in children less than 6 years old because it has not been studied in this age group.

Methylphenidate hydrochloride extended-release capsules (LA) may not be right for you or your child. Before starting methylphenidate hydrochloride extended-release capsules (LA) tell your or your child's doctor about all health conditions (or a family history of) including:

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

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

Can Methylphenidate Hydrochloride Extended-Release Capsules (LA) be taken with other medicines?

Tell your doctor about all of the medicines that you or your child take including prescription and nonprescription

Once Daily

METHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES (LA)

CII

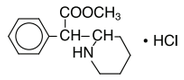
Rx Only

DESCRIPTION

Methylphenidate hydrochloride USP is a central nervous system (CNS) stimulant.

Methylphenidate hydrochloride extended-release capsules (LA) are an extended-release formulation of methylphenidate with a bi-modal release profile. Each bead-filled methylphenidate hydrochloride extended-release capsule (LA) contains half the dose as immediate-release beads and half as enteric-coated, delayed-release beads, thus providing an immediate release of methylphenidate and a second delayed release of methylphenidate. Methylphenidate hydrochloride extended-release 10, 20, 30, and 40 mg capsules (LA) provide in a single dose the same amount of methylphenidate as dosages of 5, 10, 15, or 20 mg of methylphenidate hydrochloride tablets given b.i.d.

The active substance in methylphenidate hydrochloride extended-release capsules (LA) is methyl α-phenyl-2-piperidineacetate hydrochloride, and its structural formula is



Methylphenidate hydrochloride USP is a white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

Inactive ingredients: sugar spheres (which contain sucrose and starch), hypromellose, cellulose acetate butyrate, hypromellose acetate succinate, acetyltributyl citrate, acetone, talc, and purified water. Opaque gelatin capsules contain: titanium dioxide and gelatin. The 30 and 40 mg capsules contain D&C Red #28 and FD&C Blue #1. The capsules are imprinted with black ink which contains black iron oxide, shellac and potassium hydroxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Methylphenidate hydrochloride USP, the active ingredient in methylphenidate hydrochloride extended-release capsules (LA), is a central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the *d*- and *l-threo* enantiomers. The *d-threo* enantiomer is more pharmacologically active than the *l-threo* enantiomer.

Effects on QT Interval

The effect of dexmethylphenidate hydrochloride extended-release (dexmethylphenidate, the pharmacologically active *d*-enantiomer of methylphenidate hydrochloride) on the QT interval was evaluated in a double-blind, placebo- and open label active (moxifloxacin)-controlled study following single doses of dexmethylphenidate hydrochloride extended-release 40 mg in 75 healthy volunteers. ECGs were collected up to 12 h post-dose. Fredericia's method for heart rate correction was employed to derive the corrected QT interval (QTcF). The maximum mean prolongation of QTcF intervals was <5 ms, and the upper limit of the 90% confidence interval was below 10 ms for all time matched comparisons versus placebo. This was below the threshold of clinical concern and there was no evident-exposure response relationship.

Pharmacokinetics

Absorption

Methylphenidate hydrochloride extended-release capsules (LA) produce a bi-modal plasma concentration-time profile (i.e., two distinct peaks approximately four hours apart) when orally administered to children diagnosed with ADHD and to healthy adults. The initial rate of absorption for methylphenidate hydrochloride extended-release capsules (LA) is similar to that of methylphenidate hydrochloride tablets as shown by the similar rate parameters between the two formulations, i.e., initial lag time (T_{lag}), first peak concentration (C_{max1}), and time to the first peak (T_{max1}), which is reached in 1 to 3 hours. The mean time to the interpeak minimum (T_{minip}), and time to the second peak (T_{max2}) are also similar for methylphenidate hydrochloride extended-release capsules (LA) given once daily and methylphenidate hydrochloride tablets given in two doses 4 hours apart (see Figure 1 and Table 1), although the ranges observed are greater for methylphenidate hydrochloride extended-release capsules (LA).

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

The relative bioavailability of methylphenidate hydrochloride extended-release capsules (LA) given once daily is comparable to the same total dose of methylphenidate hydrochloride tablets given in two doses 4 hours apart in both children and in adults.

Figure 1. Mean plasma concentration time-profile of methylphenidate after a single dose of Methylphenidate Hydrochloride Extended-Release Capsules (LA) 40 mg q.d. and Methylphenidate Hydrochloride Tablets 20 mg given in two doses four hours apart

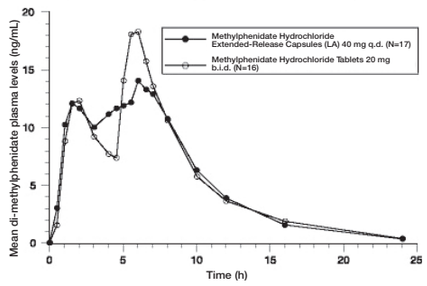


Table 1. Mean ± SD and range of pharmacokinetic parameters of methylphenidate after a single dose of Methylphenidate Hydrochloride Extended-Release Capsules (LA) and Methylphenidate Hydrochloride Tablets given in two doses 4 hours apart

Population	Children		Adult Males	
Formulation	Methylphenidate Hydrochloride Tablets	Methylphenidate Hydrochloride Extended-Release Capsules (LA)	Methylphenidate Hydrochloride Tablets	Methylphenidate Hydrochloride Extended-Release Capsules (LA)
Dose	10 mg & 10 mg	20 mg	10 mg & 10 mg	20 mg
N	21	18	9	8
T_{lag} (h)	0.24 ± 0.44	0.28 ± 0.46	1.0 ± 0.5	0.7 ± 0.2
	0 to 1	0 to 1	0.7 to 1.3	0.3 to 1.0
T_{max1} (h)	1.8 ± 0.6	2.0 ± 0.8	1.9 ± 0.4	2.0 ± 0.9
	1 to 3	1 to 3	1.3 to 2.7	1.3 to 4.0
C_{max1}(ng/mL)	10.2 ± 4.2	10.3 ± 5.1	4.3 ± 2.3	5.3 ± 0.9
	4.2 to 20.2	5.5 to 26.6	1.8 to 7.5	3.8 to 6.9
T_{minip} (h)	4.0 ± 0.2	4.5 ± 1.2	3.8 ± 0.4	3.6 ± 0.6
	4 to 5	2 to 6	3.3 to 4.3	2.7 to 4.3
C_{minip} (ng/mL)	5.8 ± 2.7	6.1 ± 4.1	1.2 ± 1.4	3.0 ± 0.8
	3.1 to 14.4	2.9 to 21.0	0.0 to 3.7	1.7 to 4.0
T_{max2} (h)	5.6 ± 0.7	6.6 ±1.5	5.9 ± 0.5	5.5 ± 0.8
	5 to 8	5 to 11	5.0 to 6.5	4.3 to 6.5
C_{max2} (ng/ml)	15.3 ± 7.0	10.2 ± 5.9	5.3 ± 1.4	6.2 ± 1.6
	6.2 to 32.8	4.5 to 31.1	3.6 to 7.2	3.9 to 8.3
$AUC_{(0-\infty)}$	102.4 ± 54.6	86.6 ± 64.0 [a]	37.8 ± 21.9	45.8 ± 10.0
(ng/mL x h-1)	40.5 to 261.6	43.3 to 301.44	14.3 to 85.3	34.0 to 61.6
$t_{1/2}$ (h)	2.5 ± 0.8	2.4 ± 0.7[a]	3.5 ± 1.9	3.3 ± 0.4
	1.8 to 5.3	1.5 to 4.0	1.3 to 7.7	3.0 to 4.2

[a] N = 15

Dose Proportionality

After oral administration of methylphenidate hydrochloride extended-release capsules (LA) 20 mg and 40 mg capsules to adults there is a slight upward trend in the methylphenidate area under the curve (AUC) and peak plasma concentrations (C_{max1} and C_{max2}).

Distribution

Binding to plasma proteins is low (10% to 33%). The volume of distribution was 2.65±1.11 L/kg for d-methylphenidate and 1.80±0.91 L/kg for l-methylphenidate.

Metabolism

The absolute oral bioavailability of methylphenidate in children was 22±8% for d-methylphenidate and 5±3% for l-methylphenidate, suggesting pronounced presystemic metabolism. Biotransformation of methylphenidate by the carboxylesterase CES1A1 is rapid and extensive leading to the main, de-esterified metabolite α-phenyl-2-piperidine acetic acid (ritalinic acid). Only small amounts of hydroxylated metabolites (e.g., hydroxymethylphenidate and hydroxyritalinic acid) are detectable in plasma. Therapeutic activity is principally due to the parent compound.

Elimination

In studies with methylphenidate hydrochloride extended-release capsules (LA) and methylphenidate hydrochloride tablets in adults, methylphenidate from methylphenidate hydrochloride tablets is eliminated from plasma with an average half-life of about 3.5 hours, (range 1.3 to 7.7 hours). In children the average half-life is about 2.5 hours, with a range of about 1.5 to 5.0 hours. The rapid half-life in both children and adults may result in unmeasurable concentrations between the morning and mid-day doses with methylphenidate hydrochloride tablets. No accumulation of methylphenidate is expected following multiple once a day oral dosing with methylphenidate hydrochloride extended-release capsules (LA). The half-life of ritalinic acid is about 3 to 4 hours.

The systemic clearance is 0.40±0.12 L/h/kg for d-methylphenidate and 0.73±0.28 L/h/kg for l-methylphenidate. After oral administration of an immediate release formulation of methylphenidate, 78% to 97% of the dose is excreted in the urine and 1% to 3% in the feces in the form of metabolites within 48 to 96 hours. Only small quantities (<1%) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as ritalinic acid (60% to 86%), the remainder being accounted for by minor metabolites

Food Effects

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

When methylphenidate hydrochloride extended-release capsules (LA) was administered with a high fat breakfast to adults, methylphenidate hydrochloride extended-release capsules (LA) had a longer lag time until absorption began and variable delays in the time until the first peak concentration, the time until the interpeak minimum, and the time until the second peak. The first peak concentration and the extent of absorption were unchanged after food relative to the fasting state, although the second peak was approximately 25% lower. The effect of a high fat lunch was not examined.

There were no differences in the pharmacokinetics of methylphenidate hydrochloride extended-release capsules (LA) when administered with applesauce, compared to administration in the fasting condition. There is no evidence of dose dumping in the presence or absence of food.

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

Special Populations

Age: The pharmacokinetics of methylphenidate hydrochloride extended-release capsules (LA) was examined in 18 children with ADHD between 7 and 12 years of age. Fifteen of these children were between 10 and 12 years of age. The time until the between peak minimum, and the time until the second peak were delayed and more variable in children compared to adults. After a 20-mg dose of methylphenidate hydrochloride extended-release capsules (LA), concentrations in children were approximately twice the concentrations observed in 18 to 35 year old adults. This higher exposure is almost completely due to the smaller body size and total volume of distribution in children, as apparent clearance normalized to body weight is independent of age.

Gender: There were no apparent gender differences in the pharmacokinetics of methylphenidate between healthy male and female adults when administered methylphenidate hydrochloride extended-release capsules (LA).

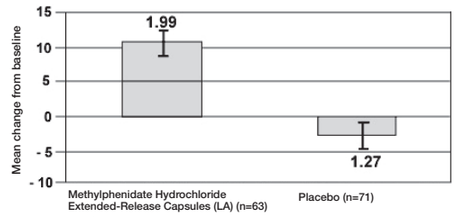
Renal Insufficiency: Methylphenidate hydrochloride extended-release capsules (LA) have not been studied in renally-impaired patients. Renal insufficiency is expected to have minimal effect on the pharmacokinetics of methylphenidate since less than 1% of a radiolabeled dose is excreted in the urine as unchanged compound, and the major metabolite (ritalinic acid), has little or no pharmacologic activity.

Hepatic Insufficiency: Methylphenidate hydrochloride extended-release capsules (LA) have not been studied in patients with hepatic insufficiency. Hepatic insufficiency is expected to have minimal effect on the pharmacokinetics of methylphenidate since it is metabolized primarily to ritalinic acid by nonmicrosomal hydrolytic esterases that are widely distributed throughout the body.

CLINICAL STUDIES

Methylphenidate hydrochloride extended-release capsules (LA) were evaluated in a randomized, double-blind, placebo-controlled, parallel group clinical study in which 134 children, ages 6 to 12, with DSM-IV diagnoses of Attention Deficit Hyperactivity Disorder (ADHD) received a single morning dose of methylphenidate hydrochloride extended-release capsules (LA) in the range of 10 to 40 mg/day, or placebo, for up to 2 weeks. The doses used were the optimal doses established in a previous individual dose titration phase. In that titration phase, 53 of 164 patients (32%) started on a daily dose of 10 mg and 111 of 164 patients (68%) started on a daily dose of 20 mg or higher. The patient's regular schoolteacher completed the Conners ADHD/DSM-IV Scale for Teachers (CADS-T) at baseline and the end of each week. The CADS-T assesses symptoms of hyperactivity and inattention. The change from baseline of the (CADS-T) scores during the last week of treatment was analyzed as the primary efficacy parameter. Patients treated with methylphenidate hydrochloride extended-release capsules (LA) showed a statistically significant improvement in symptom scores from baseline over patients who received placebo. (See Figure 2.) This demonstrates that a single morning dose of methylphenidate hydrochloride extended-release capsules (LA) exerts a treatment effect in ADHD.

Figure 2. CADS-T total subscale - Mean change from baseline*



*Error bars represent standard error of the mean

INDICATIONS AND USAGE

Methylphenidate hydrochloride extended-release capsules (LA) are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of methylphenidate hydrochloride extended-release capsules (LA) in the treatment of ADHD was established in one controlled trial of children aged 6 to 12 who met DSM-IV criteria for ADHD (see **CLINICAL PHARMACOLOGY**).

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

Special Diagnostic Considerations

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

Need for Comprehensive Treatment Program

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

Long-Term Use

The effectiveness of methylphenidate hydrochloride extended-release capsules (LA) for long-term use, i.e., for more than 2 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use methylphenidate hydrochloride extended-release capsules (LA) for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**)..

CONTRAINDICATIONS

Agitation

Methylphenidate hydrochloride extended-release capsules (LA) are contraindicated in marked anxiety, tension, and agitation, since the drug may aggravate these symptoms. .

Hypersensitivity to Methylphenidate

Methylphenidate hydrochloride extended-release capsules (LA) are contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma

Methylphenidate hydrochloride extended-release capsules (LA) are contraindicated in patients with glaucoma.

Tics

Methylphenidate hydrochloride extended-release capsules (LA) are contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome. (See **ADVERSE REACTIONS**.)

Monoamine Oxidase Inhibitors

Methylphenidate hydrochloride extended-release capsules (LA) are contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

Serious Cardiovascular Events

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

Children and Adolescents

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

Adults

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

Hypertension and Other Cardiovascular Conditions

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

Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications

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

Psychiatric Adverse Events

Pre-Existing Psychosis

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

Bipolar Illness

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

Emergence of New Psychotic or Manic Symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate.

In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3,482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression

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

Long-Term Suppression of Growth

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. In the double-blind placebo-controlled study of methylphenidate hydrochloride extended-release capsules (LA), the mean weight gain was greater for patients receiving placebo (+1.0 kg) than for patients receiving methylphenidate hydrochloride extended-release capsules (LA) (+0.1 kg). Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures

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

Visual Disturbance

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

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Use in Children Under Six Years of Age
Methylphenidate hydrochloride extended-release capsules (LA) should not be used in children under six years of age, since safety and efficacy in this age group have not been established.

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

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

Information for Patients
Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with methylphenidate and should counsel them in its appropriate use. A patient Medication Guide is available for methylphenidate hydrochloride extended-release capsules (LA). The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Drug Interactions
Methylphenidate is metabolized primarily by de-esterification (nonmicrosomal hydrolytic esterases) to ritalinic acid and not through oxidative pathways.

The effects of gastrointestinal pH alterations on the absorption of methylphenidate from methylphenidate hydrochloride extended-release capsules (LA) have not been studied. Since the modified release characteristics of methylphenidate hydrochloride extended-release capsules (LA) are pH dependent, the coadministration of antacids or acid suppressants could alter the release of methylphenidate.

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

As an inhibitor of dopamine reuptake, methylphenidate may be associated with pharmacodynamic interactions when coadministered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) as well as dopamine antagonists (antipsychotics, e.g., haloperidol).

Case reports suggest a potential interaction of methylphenidate with coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and tricyclic drugs (e.g., imipramine, clomipramine, desipramine) but pharmacokinetic interactions were not confirmed when explored at higher sample sizes. Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

Methylphenidate is not metabolized by cytochrome P450 to a clinically relevant extent. Inducers or inhibitors of cytochrome P450 are not expected to have any relevant impact on methylphenidate pharmacokinetics. Conversely, the d- and l- enantiomers of methylphenidate did not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

Methylphenidate coadministration did not increase plasma concentrations of the CYP2D6 substrate desipramine.

An interaction with the anticoagulant ethylbiscoumacetate in 4 subjects was not confirmed in a subsequent study with a higher sample size (n=12).

Other specific drug-drug interaction studies with methylphenidate have not been performed *in vivo.*

Carcinogenesis/Mutagenesis/Impairment of Fertility
In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

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

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

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended dose on a mg/kg and mg/m^2 basis, respectively.

Pregnancy
Pregnancy Category C

In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 40 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m^2 basis). When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day, offspring body weight gain was decreased at the highest dose (4 times the MRHD on a mg/m^2 basis), but no other effects on postnatal development were observed. The no effect level for pre- and postnatal development in rats was 15 mg/kg/day (equal to the MRHD on a mg/m^2 basis).

Adequate and well-controlled studies in pregnant women have not been conducted. Methylphenidate hydrochloride extended-release capsules (LA) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if methylphenidate hydrochloride extended-release capsules (LA) are administered to a nursing woman.

Pediatric Use
Long-term effects of methylphenidate in children have not been well established. Methylphenidate hydrochloride extended-release capsules (LA) should not be used in children under six years of age (see **WARNINGS**).

In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13 to 14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (12 times the MRHD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

ADVERSE REACTIONS
The clinical program for methylphenidate hydrochloride extended-release capsules (LA) consisted of six studies: two controlled clinical studies conducted in children with ADHD aged 6 to 12 years and four clinical pharmacology studies conducted in healthy adult volunteers. These studies included a total of 256 subjects; 195 children with ADHD and 61 healthy adult volunteers. The subjects received methylphenidate hydrochloride extended-release capsules (LA) in doses of 10 to 40 mg per day. Safety of methylphenidate hydrochloride extended-release capsules (LA) was assessed by evaluating frequency and nature of adverse events, routine laboratory tests, vital signs, and body weight.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, MEDRA terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Events in a Double-Blind, Placebo-Controlled Clinical Trial with Methylphenidate Hydrochloride Extended-Release Capsules (LA)
Treatment-Emergent Adverse Events

A placebo-controlled, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of methylphenidate hydrochloride extended-release capsules (LA) in children with ADHD aged 6 to 12 years. All subjects received methylphenidate hydrochloride extended-release capsules (LA) for up to 4 weeks, and had their dose optimally adjusted, prior to entering the double-blind phase of the trial. In the two-week double-blind treatment phase of this study, patients received either placebo or methylphenidate hydrochloride extended-release capsules (LA) at their individually-titrated dose (range 10 mg to 40 mg).

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

Adverse events with an incidence >5% during the initial four-week single-blind methylphenidate hydrochloride extended-release capsules (LA) titration period of this study were headache, insomnia, upper abdominal pain, appetite decreased, and anorexia.

Treatment-emergent adverse events with an incidence >2% among methylphenidate hydrochloride extended-release capsules (LA)-treated subjects, during the two-week double-blind phase of the clinical study, were as follows:

Preferred term	Methylphenidate Hydrochloride Extended-Release Capsules (LA)	Placebo
	N = 65 N (%)	N = 71 N (%)
Anorexia	2 (3.1)	0 (0.0)
Insomnia	2 (3.1)	0 (0.0)

Adverse Events Associated with Discontinuation of Treatment
In the two-week double-blind treatment phase of a placebo-controlled parallel-group study in children with ADHD, only one methylphenidate hydrochloride extended-release capsules (LA)-treated subject (1/65, 1.5%) discontinued due to an adverse event (depression).

In the single-blind titration period of this study, subjects received methylphenidate hydrochloride extended-release capsules (LA) for up to 4 weeks. During this period a total of six subjects (6/161, 3.7%) discontinued due to adverse events. The adverse events leading to discontinuation were anger (in 2 patients), hypomania, anxiety, depressed mood, fatigue, migraine and lethargy.

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

Other reactions include:

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

Gastrointestinal: abdominal pain, nausea

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

Metabolism/Nutrition: anorexia, weight loss during prolonged therapy

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

Vascular: blood pressure increased or decreased; cerebrovascular vasculitis; cerebral occlusions; cerebral hemorrhages and cerebrovascular accidents

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

Blood/Lymphatic: leukopenia and/or anemia

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

Psychiatric: transient depressed mood, aggressive behavior

Skin/Subcutaneous: scalp hair loss

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

DRUG ABUSE AND DEPENDENCE
Methylphenidate hydrochloride extended-release capsules (LA), like other products containing methylphenidate, are a Schedule II controlled substance. (See **WARNINGS** for boxed warning containing drug abuse and dependence information.)

OVERDOSAGE
Signs and Symptoms
Signs and symptoms of acute 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.

Poison Control Center
Consult with a Certified Poison Control Center regarding treatment for up-to-date guidance and advice.

Recommended Treatment
As with the management of all overdosage, the possibility of multiple drug ingestion should be considered.

When treating overdose, practitioners should bear in mind that there is a prolonged release of methylphenidate from methylphenidate hydrochloride extended-release capsules (LA).

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 or extracorporeal hemodialysis for methylphenidate overdosage has not been established; also, dialysis is considered unlikely to be of benefit due to the large volume of distribution of methylphenidate.

DOSAGE AND ADMINISTRATION
Administration of Dose
Methylphenidate hydrochloride extended-release capsules (LA) are for oral administration once daily in the morning. Methylphenidate hydrochloride extended-release capsules (LA) may be swallowed as whole capsules or alternatively may be administered by sprinkling the capsule contents on a small amount of applesauce (see specific instructions below). Methylphenidate hydrochloride extended-release capsules (LA) and/or their contents should not be crushed, chewed, or divided.

The capsules may be carefully opened and the beads sprinkled over a spoonful of applesauce. The applesauce should not be warm because it could affect the modified release properties of this formulation. The mixture of drug and applesauce should be consumed immediately in its entirety. The drug and applesauce mixture should not be stored for future use.

Dosing Recommendations
Dosage should be individualized according to the needs and responses of the patients.

Initial Treatment

The recommended starting dose of methylphenidate hydrochloride extended-release capsules (LA) is 20 mg once daily. Dosage may be adjusted in weekly 10 mg increments to a maximum of 60 mg/day taken once daily in the morning, depending on tolerability and degree of efficacy observed. Daily dosage above 60 mg is not recommended. When in the judgement of the clinician a lower initial dose is appropriate, patients may begin treatment with methylphenidate hydrochloride extended-release capsules (LA) 10 mg.

Patients Currently Receiving Methylphenidate
The recommended dose of methylphenidate hydrochloride extended-release capsules (LA) for patients currently taking methylphenidate b.i.d. or sustained release (SR) is provided below.

Previous Methylphenidate Dose	Recommended Methylphenidate Hydrochloride Extended-Release Capsule (LA) Dose
5 mg methylphenidate b.i.d.	10 mg q.d.
10 mg methylphenidate b.i.d. or 20 mg methylphenidate SR	20 mg q.d.
15 mg methylphenidate b.i.d.	30 mg q.d.
20 mg methylphenidate b.i.d. or 40 mg of methylphenidate SR	40 mg q.d.
30 mg methylphenidate b.i.d. or 60 mg methylphenidate SR	60 mg q.d.

For other methylphenidate regimens, clinical judgment should be used when selecting the starting dose. Methylphenidate hydrochloride extended-release capsule (LA) dosage may be adjusted at weekly intervals in 10 mg increments. Daily dosage above 60 mg is not recommended.

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 methylphenidate hydrochloride extended-release capsules (LA). It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use methylphenidate hydrochloride extended-release capsules (LA) for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials 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 one-month period, the drug should be discontinued.

HOW SUPPLIED
Methylphenidate Hydrochloride Extended-Release Capsules (LA)
20 mg: white/white (imprinted ◠ 200)
Bottles of 100 ..... NDC 67767-200-01
Bottles of 250 ..... NDC 67767-200-25

Methylphenidate Hydrochloride Extended-Release Capsules (LA)
30 mg: white/light blue (imprinted ◠ 201)
Bottles of 100 ..... NDC 67767-201-01
Bottles of 250 ..... NDC 67767-201-25

Methylphenidate Hydrochloride Extended-Release Capsules (LA)
40 mg: white/dark blue (imprinted ◠ 202)
Bottles of 100 ..... NDC 67767-202-01
Bottles of 250 ..... NDC 67767-202-25

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

Dispense in tight container (USP).

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

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medicines, vitamins, and herbal supplements. Methylphenidate hydrochloride extended-release capsules (LA) and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted while taking methylphenidate hydrochloride extended-release capsules (LA).

Your doctor will decide whether methylphenidate hydrochloride extended-release capsules (LA) can be taken with other medicines.

Especially tell your doctor if you or your child takes:

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

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

Do not start any new medicine while taking methylphenidate hydrochloride extended-release capsules (LA) without talking to your doctor first.

How should Methylphenidate Hydrochloride Extended-Release Capsules (LA) be taken?

- **Take methylphenidate hydrochloride extended-release capsules (LA) exactly as prescribed.** Your doctor may adjust the dose until it is right for you or your child.
- Take methylphenidate hydrochloride extended-release capsules (LA) once a day in the morning. Methylphenidate hydrochloride extended-release capsules (LA) are an extended-release capsule. It releases medicine into your body throughout the day.
- Swallow methylphenidate hydrochloride extended-release capsules (LA) capsules whole with water or other liquids. If you cannot swallow the capsule, open it and sprinkle the medicine over a spoonful of applesauce. Swallow the applesauce and medicine mixture without chewing. Follow with a drink of water or other liquid. **Never chew or crush the capsule or the medicine inside the capsule.**
- From time to time, your doctor may stop methylphenidate hydrochloride extended-release capsule (LA) treatment for a while to check ADHD symptoms.
- Your doctor may do regular checks of the blood, heart, and blood pressure while taking methylphenidate hydrochloride extended-release capsules (LA). Children should have their height and weight checked often while taking methylphenidate hydrochloride extended-release capsules (LA). Methylphenidate hydrochloride extended-release capsule (LA) treatment may be stopped if a problem is found during these check-ups.
- **If you or your child takes too much methylphenidate hydrochloride extended-release capsules (LA) or overdoses, call your doctor or poison control center right away, or get emergency treatment.**

What are possible side effects of Methylphenidate Hydrochloride Extended-Release Capsules (LA)?

See **"What is the most important information I should know about Methylphenidate Hydrochloride Extended-Release Capsules (LA)"** for information on reported heart and mental problems.

Other serious side effects include:

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

Common side effects include:

- headache
- stomach ache
- decreased appetite
- trouble sleeping

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

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

How should I store Methylphenidate Hydrochloride Extended-Release Capsules (LA)?

- Store methylphenidate hydrochloride extended-release capsules (LA) in a safe place at room temperature, 59 to 86° F (15 to 30° C).
- **Keep methylphenidate hydrochloride extended-release capsules (LA) and all medicines out of the reach of children.**

General information about Methylphenidate Hydrochloride Extended-Release Capsules (LA)

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use methylphenidate hydrochloride extended-release capsules (LA) for a condition for which it was not prescribed. Do not give methylphenidate hydrochloride extended-release capsules (LA) to other people, even if they have the same condition. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about methylphenidate hydrochloride extended-release capsules (LA). If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about methylphenidate hydrochloride extended-release capsules (LA) that was written for healthcare professionals. For more information about methylphenidate hydrochloride extended-release capsules (LA) call 1-800-432-8534.

What are the ingredients in Methylphenidate Hydrochloride Extended-Release Capsules (LA)?

Active Ingredient: methylphenidate hydrochloride USP

Inactive Ingredients: sugar spheres (which contain sucrose and starch), hypromellose, cellulose acetate butyrate, hypromellose acetate succinate, acetyltributyl citrate, acetone, talc, and purified water. Opaque gelatin capsules contain: titanium dioxide and gelatin. The 30 and 40 mg capsules contain D&C Red #28 and FD&C Blue #1. The capsules are imprinted with black ink which contains black iron oxide, shellac and potassium hydroxide.

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

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

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NDC 67767-**200**-01

℞ Only

CII

Once Daily

Methylphenidate Hydrochloride

Extended-Release Capsules (LA) 20 mg

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY.

100 capsules

EACH EXTENDED-RELEASE CAPSULE CONTAINS:
Methylphenidate Hydrochloride, USP..... 20 mg

Usual Dosage: See package insert.

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

Dispense in tight container (USP).
Store this and all drugs out of the reach of children.

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Exp. Date:

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CII

Once Daily

Methylphenidate Hydrochloride

Extended-Release Capsules (LA) 20 mg

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY.

250 capsules

EACH EXTENDED-RELEASE CAPSULE CONTAINS:
Methylphenidate Hydrochloride, USP..... 20 mg

Usual Dosage: See package insert.

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

Dispense in tight container (USP).

Store this and all drugs out of the reach of children.

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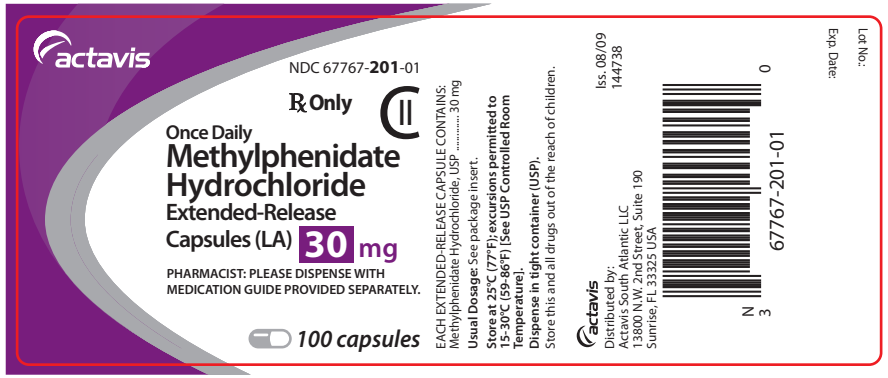
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CII
Once Daily
Methylphenidate Hydrochloride
Extended-Release
Capsules (LA) 30 mg
PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY.
100 capsules
EACH EXTENDED-RELEASE CAPSULE CONTAINS:
Methylphenidate Hydrochloride, USP ..... 30 mg
Usual Dosage: See package insert.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].
Dispense in tight container (USP).
Store this and all drugs out of the reach of children.
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℞ Only

CII

Once Daily

Methylphenidate Hydrochloride

Extended-Release Capsules (LA) 30 mg

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY.

250 capsules

EACH EXTENDED-RELEASE CAPSULE CONTAINS:
Methylphenidate Hydrochloride, USP..... 30 mg

Usual Dosage: See package insert.

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

Dispense in tight container (USP).
Store this and all drugs out of the reach of children.

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℞ Only

CII

Once Daily

Methylphenidate Hydrochloride

Extended-Release Capsules (LA) 40 mg

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY.

100 capsules

EACH EXTENDED-RELEASE CAPSULE CONTAINS: Methylphenidate Hydrochloride, USP..... 40 mg

Usual Dosage: See package insert.

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

Dispense in tight container (USP).

Store this and all drugs out of the reach of children.

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Lot No.:

Exp. Date:


actavis
NDC 67767-202-25
℞ Only
CII
Once Daily
Methylphenidate Hydrochloride
Extended-Release
Capsules (LA) 40 mg
PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY.
250 capsules
EACH EXTENDED-RELEASE CAPSULE CONTAINS:
Methylphenidate Hydrochloride, USP..... 40 mg
Usual Dosage: See package insert.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].
Dispense in tight container (USP).
Store this and all drugs out of the reach of children.
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