

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

METHYLPHENIDATE HYDROCHLORIDE tablets, for oral use, CII
Initial U.S. Approval: 1955

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

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

-----INDICATIONS AND USAGE-----
Methylphenidate hydrochloride is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorders (ADHD) and Narcolepsy (1).

-----DOSAGE AND ADMINISTRATION-----
Methylphenidate Hydrochloride Tablets, USP (2.2):

- Pediatric Patients 6 Years and Older: Start with 5 mg twice daily (before breakfast and lunch), titrating the dose weekly in 5- to 10- mg increments. Dosages above 60 mg/day are not recommended.
- Adults: Average daily dosage is 20 mg to 30 mg, administered 2 or 3 times daily, preferably 30 to 45 minutes before meals. Maximum total daily dosage is 60 mg.

-----DOSAGE FORMS AND STRENGTHS-----

- Tablets: 5 mg, 10 mg, and 20 mg (3)

-----CONTRAINDICATIONS-----

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

-----WARNINGS AND PRECAUTIONS-----

- Serious Cardiovascular Events:* Sudden death has been reported in association with CNS-stimulant treatment at usual doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ABUSE AND DEPENDENCE

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Pretreatment Screening
- 2.2 General Dosing Information
- 2.3 Dose Reduction and Discontinuation

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Potential for Abuse and Dependence
- 5.2 Serious Cardiovascular Reactions
- 5.3 Blood Pressure and Heart Rate Increases
- 5.4 Psychiatric Adverse Reactions
- 5.5 Priapism
- 5.6 Peripheral Vasculopathy, Including Raynaud's Phenomenon
- 5.7 Long-Term Suppression of Growth

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

- 7.1 Clinically Important Drug Interactions With Methylphenidate Hydrochloride

FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

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

1 INDICATIONS AND USAGE

Methylphenidate hydrochloride tablets are indicated for the treatment of:

- Attention Deficit Hyperactivity Disorders (ADHD) in pediatric patients 6 years and older and adults
- Narcolepsy

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating pediatric patients and adults with central nervous system (CNS) stimulants, including methylphenidate hydrochloride tablets, assess for the presence of cardiac disease (i.e., perform a careful history, including family history of sudden death or ventricular arrhythmia, and physical examination) [see Warnings and Precautions (5.2)]. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and periodically reevaluate the need for methylphenidate hydrochloride tablets use [see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)].

2.2 General Dosing Information

Methylphenidate Hydrochloride Tablets
Pediatric Patients 6 years and Older: Start with 5 mg orally twice daily (before breakfast and lunch). Increase dosage gradually, in increments of 5- to 10- mg weekly. Daily dosage above 60 mg is not recommended. *Adults:* Average dosage is 20 to 30 mg daily. Administer orally in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Maximum total daily dosage is 60 mg. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m. Pharmacological treatment of ADHD may be needed for extended periods. Periodically reevaluate the long-term use of methylphenidate hydrochloride tablets, and adjust dosage as needed.

2.3 Dose Reduction and Discontinuation

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

3 DOSAGE FORMS AND STRENGTHS

- Tablets
- 5 mg, Light yellow, round, biconvex, beveled edge tablets de-bossed with 'T' on one side and '173' on the other side.
 - 10 mg, White to off white, round, flat, beveled edge tablets de-bossed with 'T' and '174' with a break line on one side and plain on the other side.
 - 20 mg, Light yellow, round, flat, beveled edge tablets de-bossed with 'T' and '175' with a break line on one side and plain on the other side.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

CNS stimulants, including methylphenidate hydrochloride, other methylphenidate-containing products, and amphetamines, have a high

have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm arrhythmias, or coronary artery disease (5.2).

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

-----ADVERSE REACTIONS-----

Common adverse reactions: tachycardia, palpitations, headache, insomnia, anxiety, hyperhidrosis, weight loss, decreased appetite, dry mouth, nausea, and abdominal pain (6).

To report SUSPECTED ADVERSE REACTIONS, contact Camber Pharmaceuticals Inc., at 1-866-495-8330 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

8	USE IN SPECIFIC POPULATIONS
8.1	Pregnancy
8.2	Lactation
8.4	Pediatric Use
8.5	Geriatric Use
9	DRUG ABUSE AND DEPENDENCE
9.1	Controlled Substance
9.2	Abuse
9.3	Dependence
10	OVERDOSAGE
11	DESCRIPTION
12	CLINICAL PHARMACOLOGY
12.1	Mechanism of Action
12.2	Pharmacodynamics
12.3	Pharmacokinetics
13	NONCLINICAL TOXICOLOGY
13.1	Carcinogenesis, Mutagenesis, and Impairment of Fertility
16	HOW SUPPLIED/STORAGE AND HANDLING
17	PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [see Boxed Warning, Drug Abuse and Dependence (9.2, 9.3)].

5.2 Serious Cardiovascular Reactions

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

5.3 Blood Pressure and Heart Rate Increases

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

5.4 Psychiatric Adverse Reactions

Exacerbation of Preexisting Psychosis
CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder. *Induction of a Manic Episode in Patients with Bipolar Disorder*
CNS stimulants may induce a manic or mixed mood episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression). *New Psychotic or Manic Symptoms*
CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing methylphenidate hydrochloride. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared to 0 in placebo-treated patients.

5.5 Priapism

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

5.6 Peripheral Vasculopathy, Including Raynaud's Phenomenon

CNS stimulants, including methylphenidate hydrochloride, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in postmarketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

5.7 Long-Term Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Careful follow-up of weight and height in pediatric patients ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated pediatric patients (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.



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

6 ADVERSE REACTIONS

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

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

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

Adverse Reactions Reported With Methylphenidate Hydrochloride Infections and Infestations: nasopharyngitis
Blood and the Lymphatic System Disorders: leukopenia, thrombocytopenia, anemia
Immune System Disorders: hypersensitivity reactions, including angioedema, and anaphylaxis
Metabolism and Nutrition Disorders: decreased appetite, reduced weight gain, and suppression of growth during prolonged use in pediatric patients
Psychiatric Disorders: insomnia, anxiety, restlessness, agitation, psychosis (sometimes with visual and tactile hallucinations), depressed mood
Nervous System Disorders: headache, dizziness, tremor, dyskinesia, including choreoathetoid movements, drowsiness, convulsions, cerebrovascular disorders (including vasculitis, cerebral hemorrhages and cerebrovascular accidents), serotonin syndrome in combination with serotonergic drugs
Eye Disorders: blurred vision, difficulties in visual accommodation
Cardiac Disorders: tachycardia, palpitations, increased blood pressure, arrhythmias, angina pectoris
Respiratory, Thoracic, and Mediastinal Disorders: cough
Gastrointestinal Disorders: dry mouth, nausea, vomiting, abdominal pain, dyspepsia
Hepatobiliary Disorders: abnormal liver function, ranging from transaminase elevation to severe hepatic injury
Skin and Subcutaneous Tissue Disorders: hyperhidrosis, pruritus, urticaria, exfoliative dermatitis, scalp hair loss, erythema multiforme rash, thrombocytopenic purpura
Musculoskeletal and Connective Tissue Disorders: arthralgia, muscle cramps, rhabdomyolysis
Investigations: weight loss (adult ADHD patients)
Additional Adverse Reactions Reported with Other Methylphenidate-Containing Products

The list below shows adverse reactions not listed for methylphenidate hydrochloride that have been reported with other methylphenidate-containing products.

Blood and Lymphatic Disorders: pancytopenia
Immune System Disorders: hypersensitivity reactions, such as auricular swelling, bullous conditions, eruptions, exanthemas
Psychiatric Disorders: affect lability, mania, disorientation, and libido changes
Nervous System Disorders: migraine
Eye Disorders: diplopia, mydriasis
Cardiac Disorders: sudden cardiac death, myocardial infarction, bradycardia, extrasystole
Vascular Disorders: peripheral coldness, Raynaud's phenomenon
Respiratory, Thoracic, and Mediastinal Disorders: pharyngolaryngeal pain, dyspnea
Gastrointestinal Disorders: diarrhea, constipation
Skin and Subcutaneous Tissue Disorders: angioneurotic edema, erythema, fixed drug eruption
Musculoskeletal, Connective Tissue, and Bone Disorders: myalgia, muscle twitching

Renal and Urinary Disorders: hematuria
Reproductive System and Breast Disorders: gynecomastia
General Disorders: fatigue, hyperperexia
Urogenital Disorders: priapism

7 DRUG INTERACTIONS

7.1 Clinically Important Drug Interactions with Methylphenidate Hydrochloride

Table 1 presents clinically important drug interactions with methylphenidate hydrochloride tablets

Table 1: Clinically Important Drug Interactions with Methylphenidate Hydrochloride

Monoamine Oxidase Inhibitors (MAOI)	
<i>Clinical Impact</i>	Concomitant use of MAOIs and CNS stimulants, including methylphenidate hydrochloride can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure [see Contraindications (4)].
<i>Intervention</i>	Concomitant use of methylphenidate hydrochloride with MAOIs or within 14 days after discontinuing MAOI treatment is contraindicated.
<i>Examples</i>	selegiline, tranlylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Antihypertensive Drugs	
<i>Clinical Impact</i>	Methylphenidate hydrochloride may decrease the effectiveness of drugs used to treat hypertension [see Warnings and Precautions (5.3)].
<i>Intervention</i>	Monitor blood pressure and adjust the dosage of the antihypertensive drug as needed.
<i>Examples</i>	Potassium-sparing and thiazide diuretics, calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, centrally acting alpha-2 receptor agonists
Halogenated Anesthetics	
<i>Clinical Impact</i>	Concomitant use of halogenated anesthetics and methylphenidate hydrochloride may increase the risk of sudden blood pressure and heart rate increase during surgery.
<i>Intervention</i>	Avoid use of methylphenidate hydrochloride in patients being treated with anesthetics on the day of surgery.
<i>Examples</i>	halothane, isoflurane, enflurane, desflurane, sevoflurane
Risperidone	
<i>Clinical Impact</i>	Combined use of methylphenidate with risperidone when there is a change, whether an increase or decrease, in dosage of either or both medications, may increase the risk of extrapyramidal symptoms (EPS)
<i>Intervention</i>	Monitor for signs of EPS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications, including methylphenidate hydrochloride tablets, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for ADHD Medications at 1-866-961-2388 or visit <https://womensmentalhealth.org/adhd-medications/> Risk Summary

Published studies and postmarketing reports on methylphenidate use during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There may be risks to the fetus associated with the use of CNS stimulants use during pregnancy [see Clinical Considerations].

No effects on morphological development were observed in embryo-fetal development studies with oral administration of methylphenidate to pregnant rats and rabbits during organogenesis at doses up to 10 and 15 times, respectively, the maximum recommended human dose (MRHD) of 60 mg/day given to adolescents on a mg/m² basis. However, spina bifida was observed in rabbits at a dose 52 times the MRHD given to adolescents. A decrease in pup body weight was observed in a pre- and post-natal development study with oral administration of methylphenidate to rats throughout pregnancy and lactation at doses 6 times the MRHD given to adolescents [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

CNS stimulants, such as methylphenidate hydrochloride tablets, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

Data

Animal Data

In embryo-fetal development 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. Malformations (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 52 times the MRHD of 60 mg/day given to adolescents on a mg/m² basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (15times the MRHD given to adolescents on a mg/m² basis). There was no evidence of morphological development effects in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (10 times the MRHD of 60 mg/day given to adolescents on a mg/m² basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (3 times the MRHD on a mg/m² 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 (6 times the MRHD of 60 mg/day given to adolescents on a mg/m² 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 (~2 times the MRHD given to adolescents on a mg/m² basis).

8.2 Lactation

Risk Summary

Limited published literature, based on milk sampling from seven mothers reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. Long-term neurodevelopmental effects on infants from stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for methylphenidate hydrochloride and any potential adverse effects on the breastfed infant from methylphenidate hydrochloride or from the underlying maternal condition.

Clinical Considerations

Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

8.4 Pediatric Use

The safety and effectiveness of methylphenidate hydrochloride for the treatment of ADHD have been established in pediatric patients 6 to 17 years. The safety and effectiveness of methylphenidate hydrochloride in pediatric patients less than 6 years have not been established. The long-term efficacy of methylphenidate hydrochloride in pediatric patients has not been established.

Long-Term Suppression of Growth

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

Juvenile Animal Toxicity Data

Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 4 times the MRHD of 60 mg/day given to children on a mg/m² basis.

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 4 times the MRHD of 60 mg/day given to children on a mg/m² basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (8 times the MRHD given to children on a mg/m² basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (approximately 0.5 times the MRHD given to children on a mg/m² basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use

Methylphenidate hydrochloride has not been studied in the geriatric population.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Methylphenidate hydrochloride tablets contain methylphenidate hydrochloride, a Schedule II controlled substance.

9.2 Abuse

CNS stimulants, including methylphenidate hydrochloride tablets, have a high potential for abuse. Abuse is characterized by impaired control over drug use despite harm, and craving.

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

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

9.3 Dependence

Tolerance

Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) can occur



JOB SPECIFICATION FORM

Job #:

Customer Name:

Customer Rep:

Date Submitted:

JOB INFO

Job Name:

Type: New Design ()

Reprint ()

File Name:

JOB TYPE: () Insert

() Med Guide

() Patient Guide

Rev:

Proof #:

Grain direction:

Manufacture by:

Manufacture for:

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Final Folded size:

Finishing For Padding:

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Width: 10.625"
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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

METHYLPHENIDATE HYDROCHLORIDE tablets, for oral use, CII
Initial U.S. Approval: 1955

WARNING: ABUSE AND DEPENDENCE

- See full prescribing information for complete boxed warning.**
- CNS stimulants, including methylphenidate hydrochloride tablets, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence (5.1, 9.2, 9.3).
 - Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy (5.1, 9.2).

INDICATIONS AND USAGE

Methylphenidate hydrochloride is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorders (ADHD) and Narcolepsy (1).

DOSAGE AND ADMINISTRATION

- Methylphenidate Hydrochloride Tablets, USP (2.2):**
- Pediatric Patients 6 Years and Older: Start with 5 mg twice daily (before breakfast and lunch), titrating the dose weekly in 5- to 10- mg increments. Dosages above 60 mg/day are not recommended.
 - Adults: Average daily dosage is 20 mg to 30 mg, administered 2 or 3 times daily, preferably 30 to 45 minutes before meals. Maximum total daily dosage is 60 mg.

DOSAGE FORMS AND STRENGTHS

- Tablets: 5 mg, 10 mg, and 20 mg (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Serious Cardiovascular Events:** Sudden death has been reported in association with CNS-stimulant treatment at usual doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction

have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm arrhythmias, or coronary artery disease (5.2).

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

ADVERSE REACTIONS

Common adverse reactions: tachycardia, palpitations, headache, insomnia, anxiety, hyperhidrosis, weight loss, decreased appetite, dry mouth, nausea, and abdominal pain (6).

To report SUSPECTED ADVERSE REACTIONS, contact Camber Pharmaceuticals Inc., at 1-866-495-8330 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/21

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WARNING: ABUSE AND DEPENDENCE

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Pretreatment Screening
- 2.2 General Dosing Information
- 2.3 Dose Reduction and Discontinuation

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Potential for Abuse and Dependence
- 5.2 Serious Cardiovascular Reactions
- 5.3 Blood Pressure and Heart Rate Increases
- 5.4 Psychiatric Adverse Reactions
- 5.5 Priapism
- 5.6 Peripheral Vasculopathy, Including Raynaud's Phenomenon
- 5.7 Long-Term Suppression of Growth

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

- 7.1 Clinically Important Drug Interactions With Methylphenidate Hydrochloride

FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

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

1 INDICATIONS AND USAGE

Methylphenidate hydrochloride tablets are indicated for the treatment of: • Attention Deficit Hyperactivity Disorders (ADHD) in pediatric patients 6 years and older and adults

- Narcolepsy

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

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

Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and periodically reevaluate the need for methylphenidate hydrochloride tablets use [see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)].

2.2 General Dosing Information

Methylphenidate Hydrochloride Tablets

Pediatric Patients 6 years and Older: Start with 5 mg orally twice daily (before breakfast and lunch). Increase dosage gradually, in increments of 5- to 10- mg weekly. Daily dosage above 60 mg is not recommended.

Adults: Average dosage is 20 to 30 mg daily. Administer orally in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Maximum total daily dosage is 60 mg. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m. Pharmacological treatment of ADHD may be needed for extended periods. Periodically reevaluate the long-term use of methylphenidate hydrochloride tablets, and adjust dosage as needed.

2.3 Dose Reduction and Discontinuation

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

3 DOSAGE FORMS AND STRENGTHS

Tablets

- 5 mg, Light yellow, round, biconvex, beveled edge tablets de-bossed with 'T' on one side and '173' on the other side.
- 10 mg, White to off white, round, flat, beveled edge tablets de-bossed with 'T' and '174' with a break line on one side and plain on the other side.
- 20 mg, Light yellow, round, flat, beveled edge tablets de-bossed with 'T' and '175' with a break line on one side and plain on the other side.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

CNS stimulants, including methylphenidate hydrochloride, other methylphenidate-containing products, and amphetamines, have a high

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [see Boxed Warning, Drug Abuse and Dependence (9.2, 9.3)].

5.2 Serious Cardiovascular Reactions

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

5.3 Blood Pressure and Heart Rate Increases

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

5.4 Psychiatric Adverse Reactions

Exacerbation of Preexisting Psychosis

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder. **Induction of a Manic Episode in Patients with Bipolar Disorder** CNS stimulants may induce a manic or mixed mood episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms

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

5.5 Priapism

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

5.6 Peripheral Vasculopathy, Including Raynaud's Phenomenon

CNS stimulants, including methylphenidate hydrochloride, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in postmarketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

5.7 Long-Term Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Careful follow-up of weight and height in pediatric patients ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated pediatric patients (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

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

6 ADVERSE REACTIONS

- The following are discussed in more detail in other sections of the labeling:
- Abuse and Dependence [see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)]
 - Known hypersensitivity to methylphenidate or other ingredients of methylphenidate hydrochloride tablets [see Contraindications (4)]
 - Hypertensive crisis with Concomitant Use of Monoamine Oxidase Inhibitors [see Contraindications (4), Drug Interactions (7.1)]
 - Serious Cardiovascular Reactions [see Warnings and Precautions (5.2)]
 - Blood Pressure and Heart Rate Increases [see Warnings and Precautions (5.3)]
 - Psychiatric Adverse Reactions [see Warnings and Precautions (5.4)]
 - Priapism [see Warnings and Precautions (5.5)]
 - Peripheral Vasculopathy, Including Raynaud's Phenomenon [see Warnings and Precautions (5.6)]
 - Long-Term Suppression of Growth [see Warnings and Precautions (5.7)]

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

Adverse Reactions Reported With Methylphenidate Hydrochloride

Infections and Infestations:

nasopharyngitis

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

Immune System Disorders: hypersensitivity reactions, including angioedema, and anaphylaxis

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

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

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

Eye Disorders: blurred vision, difficulties in visual accommodation

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

Respiratory, Thoracic, and Mediastinal Disorders: cough

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

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

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

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

Investigations: weight loss (adult ADHD patients)

Additional Adverse Reactions Reported with Other Methylphenidate-Containing Products

The list below shows adverse reactions not listed for methylphenidate hydrochloride that have been reported with other methylphenidate-containing products.

Blood and Lymphatic Disorders: pancytopenia

Immune System Disorders: hypersensitivity reactions, such as auricular swelling, bullous conditions, eruptions, exanthemas

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

Nervous System Disorders: migraine

Eye Disorders: diplopia, mydriasis

Cardiac Disorders: sudden cardiac death, myocardial infarction, bradycardia, extrasystole

Vascular Disorders: peripheral coldness, Raynaud's phenomenon

Respiratory, Thoracic, and Mediastinal Disorders: pharyngolaryngeal pain, dyspnea

Gastrointestinal Disorders: diarrhea, constipation

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

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

Renal and Urinary Disorders: hematuria

Reproductive System and Breast Disorders: gynecomastia

General Disorders: fatigue, hyperpyrexia

Urogenital Disorders: priapism

7 DRUG INTERACTIONS

7.1 Clinically Important Drug Interactions with Methylphenidate Hydrochloride

Table 1 presents clinically important drug interactions with methylphenidate hydrochloride tablets

Table 1: Clinically Important Drug Interactions with Methylphenidate Hydrochloride

Monoamine Oxidase Inhibitors (MAOI)	
Clinical Impact	Concomitant use of MAOIs and CNS stimulants, including methylphenidate hydrochloride can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure [see Contraindications (4)].
Intervention	Concomitant use of methylphenidate hydrochloride with MAOIs or within 14 days after discontinuing MAOI treatment is contraindicated.
Examples	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Antihypertensive Drugs	
Clinical Impact	Methylphenidate hydrochloride may decrease the effectiveness of drugs used to treat hypertension [see Warnings and Precautions (5.3)].
Intervention	Monitor blood pressure and adjust the dosage of the antihypertensive drug as needed.
Examples	Potassium-sparing and thiazide diuretics, calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, centrally acting alpha-2 receptor agonists
Halogenated Anesthetics	
Clinical Impact	Concomitant use of halogenated anesthetics and methylphenidate hydrochloride may increase the risk of sudden blood pressure and heart rate increase during surgery.
Intervention	Avoid use of methylphenidate hydrochloride in patients being treated with anesthetics on the day of surgery.
Examples	halothane, isoflurane, enflurane, desflurane, sevoflurane
Risperidone	
Clinical Impact	Combined use of methylphenidate with risperidone when there is a change, whether an increase or decrease, in dosage of either or both medications, may increase the risk of extrapyramidal symptoms (EPS)
Intervention	Monitor for signs of EPS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications, including methylphenidate hydrochloride tablets, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for ADHD Medications at 1-866-961-2388 or visit <https://womensmentalhealth.org/adhd-medications/RiskSummary>

Published studies and postmarketing reports on methylphenidate use during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There may be risks to the fetus associated with the use of CNS stimulants use during pregnancy (see Clinical Considerations).

No effects on morphological development were observed in embryo-fetal development studies with oral administration of methylphenidate to pregnant rats and rabbits during organogenesis at doses up to 10 and 15 times, respectively, the maximum recommended human dose (MRHD) of 60 mg/day given to adolescents on a mg/m² basis. However, spina bifida was observed in rabbits at a dose 52 times the MRHD to adolescents. A decrease in pup body weight was observed in a pre- and post-natal development study with oral administration of methylphenidate to rats throughout pregnancy and lactation at doses 6 times the MRHD given to adolescents (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

CNS stimulants, such as methylphenidate hydrochloride tablets, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

Data

Animal Data

In embryo-fetal development 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. Malformations (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 52 times the MRHD of 60 mg/day given to adolescents on a mg/m² basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (15times the MRHD given to adolescents on a mg/m² basis). There was no evidence of morphological development effects in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (10 times the MRHD of 60 mg/day given to adolescents on a mg/m² basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (3 times the MRHD on a mg/m² 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 (6 times the MRHD of 60 mg/day given to adolescents on a mg/m² 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 (~2 times the MRHD given to adolescents on a mg/m² basis).

8.2 Lactation

Risk Summary

Limited published literature, based on milk sampling from seven mothers reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. Long-term neurodevelopmental effects on infants from stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for methylphenidate hydrochloride and any potential adverse effects on the breastfed infant from methylphenidate hydrochloride or from the underlying maternal condition.

Clinical Considerations

Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

8.4 Pediatric Use

The safety and effectiveness of methylphenidate hydrochloride for the treatment of ADHD have been established in pediatric patients 6 to 17 years. The safety and effectiveness of methylphenidate hydrochloride in pediatric patients less than 6 years have not been established.

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

Long-Term Suppression of Growth

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

Juvenile Animal Toxicity Data

Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 4 times the MRHD of 60 mg/day given to children on a mg/m² basis.

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 4 times the MRHD of 60 mg/day given to children on a mg/m² basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (8 times the MRHD given to children on a mg/m² basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (approximately 0.5 times the MRHD given to children on a mg/m² basis). The clinical significance of the long-term behavioral