HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use methylphenidate hydrochloride extended-release tablets safely and effectively. See full prescribing information for methylphenidate hydrochloride extended-release tablets.

Methylphenidate hydrochloride extended-release tablets for oral use, CII

Initial U.S. Approval: 2000

WARNING: ABUSE, MISUSE, AND ADDICTION

See full prescribing information for complete boxed warning.

Methylphenidate hydrochloride extended-release tablets have a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including methylphenidate hydrochloride extended-release tablets, can result in overdose and death (5.1, 9.2, 10):

- **Before prescribing methylphenidate hydrochloride extended-release tablets, assess each patient's risk for abuse, misuse, and addiction.**
- **Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug.**
- **Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction.**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	09/2025
Warnings and Precautions (5.7)	09/2025

----------INDICATIONS AND USAGE----------

Methylphenidate hydrochloride extended-release tablets are a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults (up to the age of 65 years) and pediatric patients 6 years of age and older (1).

Limitations of Use

The use of methylphenidate hydrochloride extended-release tablets is not recommended in pediatric patients younger than 6 years of age because they had higher plasma exposure and a higher incidence of adverse reactions (e.g., weight loss) than patients 6 years and older at the same dosage (5.7, 8.4).

----------DOSAGE AND ADMINISTRATION ----------

- Administer once daily in the morning with or without food. (2.2)
- Swallow whole with liquid. Do not chew, divide, or crush. (2.2)
- Recommended dosage for patients new to methylphenidate (2.3):
  - Pediatric patients 6 to 17 years
    - Starting dosage is 18 mg once daily. Dosage may be increased by 18 mg once per day at weekly intervals.
    - Maximum dosage for pediatric patients 6 to 12 years: 54 mg once daily.
    - Maximum dosage for pediatric patients 13 to 17 years: 72 mg once daily.
  - Adults (up to 65 years)
    - Starting dosage is 18 mg or 36 mg once daily. Dosage may be increased by 18 mg once daily at weekly intervals.
    - Maximum dosage: 72 mg once daily.

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

Extended-release tablets:18 mg, 27 mg, 36 mg, 45 mg, 54 mg, 63 mg, and 72 mg (3)

----------CONTRAINDICATIONS ----------

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

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

- Risks to Patients with Serious Cardiac Disease: Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or serious cardiac disease. (5.2)
- Increased Blood Pressure and Heart Rate: Monitor blood pressure and pulse. (5.3)
- Psychiatric Adverse Reactions: Prior to initiating methylphenidate hydrochloride extended-release tablets, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing methylphenidate hydrochloride extended-release tablets. (5.4)
- Priapism: If abnormally sustained or frequent and painful erections occur, patients should seek immediate medical attention. (5.5)
- Peripheral Vasculopathy, including Raynaud's Phenomenon: Careful observation for digital changes is necessary during methylphenidate hydrochloride extended-release tablets treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy. (5.6)
- Long-Term Suppression of Growth in Pediatric Patients: Closely monitor growth (height and weight) in pediatric patients. Pediatric patients not growing or gaining weight as expected may need to have their treatment interrupted. (5.7)
- Gastrointestinal Obstruction: Avoid use with preexisting GI narrowing. (5.8)
- Acute Angle Closure Glaucoma: Methylphenidate hydrochloride extended-release tablets-treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist. (5.9)
- Increased Intraocular Pressure (IOP) and Glaucoma: Prescribe methylphenidate hydrochloride extended-release tablets to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Closely monitor patients with a history of increased IOP or open angle glaucoma. (5.10)
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome: Before initiating methylphenidate hydrochloride extended-release tablets, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome. Discontinue treatment if clinically appropriate. (5.11)

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

The most common adverse reactions (>5%) were:
Pediatric patients 6 to 17 years: abdominal pain upper (6.1)
Adults: decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, and hyperhidrosis (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Trigen Laboratories, LLC at 1-800-444-5164 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)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2025

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE, MISUSE, AND ADDICTION

Methylphenidate hydrochloride extended-release tablets have a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including methylphenidate hydrochloride extended-release tablets, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing methylphenidate hydrochloride extended-release tablets, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug. Throughout methylphenidate hydrochloride extended-release tablets treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction *[see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.2)]*.

1 INDICATIONS AND USAGE

Methylphenidate hydrochloride extended-release tablets are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults (up to the age of 65 years) and pediatric patients 6 years of age and older *[*see *Clinical Studies (14)]*.

Limitations of Use
The use of methylphenidate hydrochloride extended-release tablets is not recommended in pediatric patients younger than 6 years of age because they had higher plasma exposure and a higher incidence of adverse reactions (e.g., weight loss) than patients 6 years and older at the same dosage *[see Warnings and Precautions (5.7), Use in Specific Populations (8.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating patients with methylphenidate hydrochloride extended-release tablets assess:

- for the presence of cardiac disease (i.e., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) *[see Warnings and Precautions (5.2)]*.
- the family history and clinically evaluate patients for motor or verbal tics or Tourette's syndrome before initiating methylphenidate hydrochloride extended-release tablets *[see Warnings and Precautions (5.11)]*.

2.2 General Administration Information

Administer methylphenidate hydrochloride extended-release tablets orally once daily in the morning with or without food.

Swallow methylphenidate hydrochloride extended-release tablets whole with liquid. Do not chew, divide, or crush *[see Warnings and Precautions (5.8)]*.

2.3 Dosage Recommendations for Patients New to Methylphenidate

Table 1 includes the starting dosage and dosage recommendations for methylphenidate hydrochloride extended-release tablets in pediatric patients 6 to 17 years and adults who are not currently taking methylphenidate or other stimulants.

Table 1: Dosage Recommendations for methylphenidate hydrochloride extended-release tablets in Pediatric Patients 6 to 17 years and Adults

Patient Population	Methylphenidate hydrochloride extended-release tablets Recommended Starting Dosage	Methylphenidate hydrochloride extended-release tablets Dosage Range

Pediatric patients 6 to 12 years	18 mg once daily	18 mg to 54 mg once daily
13 to 17 years	18 mg once daily	18 mg to 72 mg once daily (not to exceed 2 mg/kg/day)
Adults 18 (up to 65 years)	18 mg or 36 mg once daily	18 mg to 72 mg once daily

2.4 Dosage Recommendations for Patients Currently Using Methylphenidate

The recommended starting dosage of methylphenidate hydrochloride extended-release tablets for patients who are currently taking methylphenidate twice daily or three times daily at doses of 10 mg to 60 mg daily is provided in Table 2.

Table 2: Recommended Starting Dosage when Converting from Methylphenidate Regimens to methylphenidate hydrochloride extended-release tablets

Current Methylphenidate Daily Dosage	**Recommended Starting Dosage of Methylphenidate hydrochloride extended-release tablets**
5 mg methylphenidate twice daily or three times daily	18 mg once daily in the morning
10 mg methylphenidate twice daily or three times daily	36 mg once daily in the morning
15 mg methylphenidate twice daily or three times daily	54 mg once daily in the morning
20 mg methylphenidate twice daily or three times daily	72 mg once daily in the morning

2.5 Dose Titration

Doses may be increased in 18 mg increments at weekly intervals for patients who have not achieved clinical response at a lower dose. Daily dosages above 54 mg in pediatric patients 6 to 12 years and above 72 mg in pediatric patients 13 to 17 years have not been studied and are not recommended. Daily dosages above 72 mg are not recommended in adults.

Dosage strengths of 27 mg, 45 mg, and 63 mg are available for additional titration options based on clinical response.

2.6 Dosage Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse reaction occur, reduce the dosage, or, if necessary, discontinue methylphenidate hydrochloride extended-release tablets.

If improvement is not observed after appropriate dosage adjustment over a one-month period, discontinue methylphenidate hydrochloride extended-release tablets.

3 DOSAGE FORMS AND STRENGTHS

Methylphenidate hydrochloride extended-release tablets are available in the following strengths:

- 18 mg: yellow with “TL706” imprinted in black ink
- 27 mg: gray with “TL707” imprinted in black ink
- 36 mg: white with “TL708” imprinted in black ink
- 45 mg: pink with “TL711” imprinted in black ink
- 54 mg: pink with “TL709” imprinted in black ink
- 63 mg: orange with “TL700” imprinted in black ink and

- 72 mg: blue with “TL710” imprinted in black ink.

4 CONTRAINDICATIONS

Methylphenidate hydrochloride extended-release tablets are contraindicated in patients:

- with a known hypersensitivity to methylphenidate or other components of methylphenidate hydrochloride extended-release tablets. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other methylphenidate products *[see Adverse Reactions (6.2)]*.
- receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs), and also within 14 days following discontinuation of treatment with a MAOI, because of the risk of hypertensive crisis *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Abuse, Misuse, and Addiction

Methylphenidate hydrochloride extended-release tablets have a high potential for abuse and misuse. The use of methylphenidate hydrochloride extended-release tablets exposes individuals to the risks of abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Methylphenidate hydrochloride extended-release tablets can be diverted for non-medical use into illicit channels or distribution *[see Drug Abuse and Dependence (9.2, 9.3)]*. Misuse and abuse of CNS stimulants, including methylphenidate hydrochloride extended-release tablets, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing methylphenidate hydrochloride extended-release tablets, assess each patient’s risk for abuse, misuse, and addiction. Educate patients and their families about these risks and proper disposal of any unused drug. Advise patients to store methylphenidate hydrochloride extended-release tablets in a safe place, preferably locked, and instruct patients to not give methylphenidate hydrochloride extended-release tablets to anyone else. Throughout methylphenidate hydrochloride extended-release tablets treatment, reassess each patient’s risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

5.2 Risks to Patients with Serious Cardiac Disease

Sudden death has been reported in patients with structural cardiac abnormalities or other serious cardiac disease who were taking CNS stimulants at the recommended ADHD dosage.

Avoid methylphenidate hydrochloride extended-release tablets use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease.

5.3 Increased Blood Pressure and Heart Rate

CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mm Hg) and heart rate (mean increase approximately 3 to 6 bpm) *[see Adverse Reactions (6.1)]*. Some patients may have larger increases.

Monitor all methylphenidate hydrochloride extended-release tablets-treated patients for hypertension and tachycardia.

5.4 Psychiatric Adverse Reactions

Exacerbation of Pre-existing 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 episode in patients. Prior to initiating methylphenidate hydrochloride extended-release tablets treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms, a family history of suicide, bipolar disorder, and depression).

New Psychotic or Manic Symptoms

CNS stimulants, at the recommended dosage, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. 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% of placebo-treated patients. If such symptoms occur, consider discontinuing methylphenidate hydrochloride extended-release tablets.

5.5 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate use, including another formulation of methylphenidate hydrochloride extended-release tablets, in both adult and pediatric male patients *[see Adverse Reactions (6.2)]*. Although priapism was not reported with methylphenidate initiation, it developed after some time on methylphenidate, often subsequent to an increase in dosage. Priapism also occurred during a methylphenidate withdrawal (drug holidays or during discontinuation).

Methylphenidate hydrochloride extended-release tablets-treated 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, such as methylphenidate hydrochloride extended-release tablets, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, sequelae have included digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports and at the therapeutic dosage in all age groups throughout the course of treatment. Signs and symptoms generally improved after reduction or discontinuation of the CNS stimulant.

Careful observation for digital changes is necessary during methylphenidate hydrochloride extended-release tablets treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for methylphenidate hydrochloride extended-release tablets-treated patients who develop signs or symptoms of peripheral vasculopathy.

5.7 Long-Term Suppression of Growth in Pediatric Patients

Methylphenidate hydrochloride extended-release tablets are not approved for use and are not recommended in pediatric patients below 6 years of age *[see Use in Specific Populations (8.4)]*.

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 nonmedication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and nonmedication-treated pediatric patients over 36 months (to the ages of 10 to 13 years), suggests that pediatric patients who received methylphenidate for 7 days per week throughout the year had 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 development period.

Closely monitor growth (weight and height) in methylphenidate hydrochloride extended-release tablets-treated pediatric patients. Pediatric patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

5.8 Potential for Gastrointestinal Obstruction

Because the methylphenidate hydrochloride extended-release tablet is nondeformable and does not appreciably change in shape in the GI tract, methylphenidate hydrochloride extended-release tablets should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudo-obstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the extended-release design of the tablet, methylphenidate hydrochloride extended-release tablets should be used only in patients who are able to swallow the tablet whole *[see Patient Counseling Information (17)]*.

5.9 Acute Angle Closure Glaucoma

There have been reports of angle closure glaucoma associated with methylphenidate treatment. Although the mechanism is not clear, methylphenidate hydrochloride extended-release tablets-treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist.

5.10 Increased Intraocular Pressure and Glaucoma

There have been reports of an elevation of intraocular pressure (IOP) associated with methylphenidate treatment *[see Adverse Reactions (6.2)]*.

Prescribe methylphenidate hydrochloride extended-release tablets to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Closely monitor methylphenidate hydrochloride extended-release tablets-treated patients with a history of abnormally increased IOP or open angle glaucoma.

5.11 Motor and Verbal Tics, and Worsening of Tourette's Syndrome

CNS stimulants, including methylphenidate, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported *[see Adverse Reactions (6.2)]*.

Before initiating methylphenidate hydrochloride extended-release tablets, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor methylphenidate hydrochloride extended-release tablets-treated patients for the emergence or worsening of tics or Tourette's syndrome, and discontinue treatment if clinically appropriate.

6 ADVERSE REACTIONS

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

- Abuse, Misuse, and Addiction *[see Box Warning, Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.2, 9.3)]*
- Known hypersensitivity to methylphenidate or other ingredients *[see Contraindications (4)]*
- Hypertensive crisis when used concomitantly with monoamine oxidase inhibitors *[see Contraindications (4) and Drug Interactions (7.1)]*
- Risks to Patients with Serious Cardiac Disease *[see Warnings and Precautions (5.2)]*
- Increased Blood Pressure and Heart Rate *[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 in Pediatric Patients *[see Warnings and Precautions (5.7)]*
- Potential for Gastrointestinal Obstruction *[see Warnings and Precautions (5.8)]*
- Acute Angle Closure Glaucoma *[see Warnings and Precautions (5.9)]*
- Increased Intraocular Pressure and Glaucoma *[see Warnings and Precautions (5.10)]*
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience

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

The safety of methylphenidate hydrochloride extended-release tablets for the treatment of ADHD is based on adequate and well-controlled studies of another formulation of methylphenidate hydrochloride extended-release tablets. Below is a

display of adverse reactions from those adequate and well-controlled studies in ADHD.

Adults and pediatric patients 6 to 17 years with ADHD were evaluated in six controlled clinical studies and eleven open-label clinical studies (see Table 3). Safety was assessed by collecting adverse reactions, vital signs, weights, and electrocardiograms (ECGs), and by performing physical examinations and laboratory analyses. A total of 3,906 patients participated in the clinical trials.

Table 3: Exposure in Double-Blind and Open-Label Clinical Studies of Another Formulation of Methylphenidate Hydrochloride Extended-Release Tablets

Patient Population	N	Dosage Range
Pediatric patients 6 to 12 years	2216	18 mg to 54 mg once daily
Pediatric patients 13 to 17 years	502	18 mg to 72 mg once daily
Adults	1188	18 mg to 108 mg* once daily

* 108 mg is 1.5 times the maximum recommended dosage of methylphenidate hydrochloride extended-release tablets.

The most common adverse reactions in double-blind clinical trials (>5%) were:

- Pediatric patients 6 to 17 years: abdominal pain upper (see Table 4).
- Adults: decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, and hyperhidrosis (see Table 5).

The most common adverse reactions associated with discontinuation (≥1%) from either pediatric or adult clinical trials were anxiety, irritability, insomnia, and blood pressure increased.

Adverse reactions in either the pediatric or adult double-blind adverse reactions tables may be relevant for both patient populations.

Pediatric Patients 6 to 17 Years

Table 4 lists the adverse reactions reported in 1% or more of another formulation of methylphenidate hydrochloride extended-release tablet-treated pediatric patients (6 to 17 years) in four placebo-controlled, double-blind clinical trials.

Table 4: Adverse Reactions Reported by ≥1% of Pediatric Patients (6 to 17 years) Treated with Another Formulation of Methylphenidate Hydrochloride Extended-release Tablets in Four Placebo-Controlled, Double-Blind Clinical Trials

System/Organ Class Adverse Reaction	Another Formulation of Methylphenidate Hydrochloride Extended-release Tablets (n=321) %	Placebo (n=318) %
Gastrointestinal Disorders		
Abdominal pain upper	6.2	3.8
Vomiting	2.8	1.6
General Disorders and Administration Site Conditions		
Pyrexia	2.2	0.9
Infections and Infestations		
Nasopharyngitis	2.8	2.2
Nervous System Disorders		
Dizziness	1.9	0
Psychiatric Disorders		
Insomnia*	2.8	0.3
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1.9	0.9
Oropharyngeal pain	1.2	0.9

* Terms of Initial insomnia (methylphenidate hydrochloride extended-release tablets =0.6%) and Insomnia (methylphenidate hydrochloride extended-release tablets =2.2%) are combined into Insomnia.

Adults

Table 5 lists the adverse reactions reported in 1% or more of adults treated with another formulation of methylphenidate hydrochloride extended-release tablets in two placebo-controlled, double-blind clinical trials.

Table 5: Adverse Reactions Reported by ≥1% of Adults Treated with Another Formulation of Methylphenidate Hydrochloride Extended-release Tablets in Two Placebo-Controlled, Double-Blind Clinical Trials*

System/Organ Class Adverse Reaction	Another Formulation of Methylphenidate Hydrochloride Extended-release Tablets (n=415) %	Placebo (n=212) %
Cardiac Disorders		
Tachycardia	4.8	0
Palpitations	3.1	0.9
Ear and Labyrinth Disorders		
Vertigo	1.7	0
Eye Disorders		
Vision blurred	1.7	0.5
Gastrointestinal Disorders		
Dry mouth	14.0	3.8
Nausea	12.8	3.3
Dyspepsia	2.2	0.9
Vomiting	1.7	0.5
Constipation	1.4	0.9
General Disorders and Administration Site Conditions		
Irritability	5.8	1.4
Infections and Infestations		
Upper respiratory tract infection	2.2	0.9
Investigations		
Weight decreased	6.5	3.3
Metabolism and Nutrition Disorders		
Decreased appetite	25.3	6.6
Anorexia	1.7	0
Musculoskeletal and Connective Tissue Disorders		
Muscle tightness	1.9	0
Nervous System Disorders		
Headache	22.2	15.6
Dizziness	6.7	5.2
Tremor	2.7	0.5
Paresthesia	1.2	0
Sedation	1.2	0
Tension headache	1.2	0.5
Psychiatric Disorders		
Insomnia	12.3	6.1
Anxiety	8.2	2.4
Initial insomnia	4.3	2.8
Depressed mood	3.9	1.4
Nervousness	3.1	0.5
Restlessness	3.1	0

Agitation	2.2	0.5
Aggression	1.7	0.5
Bruxism	1.7	0.5
Depression	1.7	0.9
Libido decreased	1.7	0.5
Affect lability	1.4	0.9
Confusional state	1.2	0.5
Tension	1.2	0.5
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal pain	1.7	1.4
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	5.1	0.9

* Included doses up to 108 mg (1.5 times the maximum recommended dosage of methylphenidate hydrochloride extended-release tablets).

Adverse Reactions Observed in Clinical Trials with Another Formulation of Methylphenidate Hydrochloride Extended-release Tablets

This section includes adverse reactions reported with use of another formulation of methylphenidate hydrochloride extended-release tablets in double-blind trials that do not meet the criteria specified for Table 4 or Table 5 and all adverse reactions reported by the other formulation of methylphenidate hydrochloride extended-release tablets-treated patients who participated in open-label and postmarketing clinical trials.

Blood and Lymphatic System Disorders: Leukopenia

Eye Disorders: Accommodation disorder, Dry eye

Vascular Disorders: Hot flush

Gastrointestinal Disorders: Abdominal discomfort, Abdominal pain, Diarrhea

General Disorders and Administrative Site Conditions: Asthenia, Fatigue, Feeling jittery, Thirst

Infections and Infestations: Sinusitis

Investigations: Alanine aminotransferase increased, Blood pressure increased, Cardiac murmur, Heart rate increased

Musculoskeletal and Connective Tissue Disorders: Muscle spasms

Nervous System Disorders: Lethargy, Psychomotor hyperactivity, Somnolence

Psychiatric Disorders: Anger, Hypervigilance, Mood altered, Mood swings, Panic attack, Sleep disorder, Tearfulness, Tic

Reproductive System and Breast Disorders: Erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea

Skin and Subcutaneous Tissue Disorders: Rash, Rash macular

Vascular Disorders: Hypertension

Discontinuation Due to Adverse Reactions

Adverse reactions in the four placebo-controlled studies of pediatric patients (6 to 17 years) leading to discontinuation occurred in 2 patients (0.6%) treated with another formulation of methylphenidate hydrochloride extended-release tablets including depressed mood (1, 0.3%) and headache and insomnia (1, 0.3%), and 6 placebo patients (1.9%) including headache and insomnia (1, 0.3%), irritability (2, 0.6%), headache (1, 0.3%), psychomotor hyperactivity (1, 0.3%), and tic (1, 0.3%).

In the two placebo-controlled studies of adults, 25 patients (6.0%) treated with another formulation of methylphenidate hydrochloride extended-release tablets and 6 placebo patients (2.8%) discontinued due to an adverse reaction. Incidence of >0.5% in patients treated with another formulation of methylphenidate hydrochloride extended-release tablets included anxiety (1.7%), irritability (1.4%), blood pressure increased (1.0%), and nervousness (0.7%). In placebo patients, blood pressure increased and depressed mood had an incidence of >0.5% (0.9%).

In the eleven open-label studies of pediatric patients and adults, 266 patients (7.0%) treated with another formulation of methylphenidate hydrochloride extended-release tablets discontinued due to an adverse reaction. Incidence of >0.5% included insomnia (1.2%), irritability (0.8%), anxiety (0.7%), decreased appetite (0.7%), and tic (0.6%).

Tics

In a long-term uncontrolled study (n=432 pediatric patients 6 to 12 years), the cumulative incidence of new onset of tics was 9% after 27 months of treatment with another formulation of methylphenidate hydrochloride extended-release tablets.

In a second uncontrolled study (n=682 pediatric patients 6 to 12 years) the cumulative incidence of new-onset tics was 1% (9/682). The treatment period was up to 9 months with mean treatment duration of 7.2 months.

Blood Pressure and Heart Rate Increases

In the laboratory classroom clinical trials in pediatric patients 6 to 12 years (Studies 1 and 2), both another formulation of methylphenidate hydrochloride extended-release tablets once daily and methylphenidate three times daily increased resting pulse by an average of 2 to 6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1 to 4 mm Hg during the day, relative to placebo. In the placebo-controlled trial in pediatric patients 13 to 17 years (Study 4), mean increases from baseline in resting pulse rate were observed with another formulation of methylphenidate hydrochloride extended-release tablets and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for another formulation of methylphenidate hydrochloride extended-release tablets and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively. In one placebo-controlled study in adults (Study 6), dose-dependent mean increases of 3.9 to 9.8 bpm from baseline in standing pulse rate were observed with another formulation of methylphenidate hydrochloride extended-release tablets at the end of the double-blind treatment vs. an increase of 2.7 beats/minute with placebo. Mean changes from baseline in standing blood pressure at the end of double-blind treatment ranged from 0.1 to 2.2 mm Hg (systolic) and -0.7 to 2.2 mm Hg (diastolic) for another formulation of methylphenidate hydrochloride extended-release tablets and was 1.1 mm Hg (systolic) and -1.8 mm Hg (diastolic) for placebo. In a second placebo-controlled study in adults (Study 5), mean changes from baseline in resting pulse rate were observed for another formulation of methylphenidate hydrochloride extended-release tablets and placebo at the end of the double-blind treatment (3.6 and –1.6 beats/minute, respectively). Mean changes from baseline in blood pressure at the end of the double–blind treatment for another formulation of methylphenidate hydrochloride extended-release tablets and placebo-treated patients were –1.2 and –0.5 mm Hg (systolic) and 1.1 and 0.4 mm Hg (diastolic), respectively *[see Warnings and Precautions (5.3)]*.

6.2 Postmarketing Experience

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

Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura

Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystoles, Supraventricular tachycardia, Ventricular extrasystoles

Eye Disorders: Diplopia, Increased intraocular pressure, Mydriasis, Visual impairment

General Disorders: Chest pain, Chest discomfort, Drug effect decreased, Hyperpyrexia, Therapeutic response decreased

Hepatobiliary Disorders: Hepatocellular injury, Acute hepatic failure

Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions, and Exanthemas NEC

Investigations: Blood alkaline phosphatase increased, Blood bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal

Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis

Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia, Serotonin syndrome in combination with serotonergic drugs, Motor and Verbal Tics

Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Mania, Logorrhea, Libido changes

Reproductive System and Breast Disorders: Priapism

Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema

Vascular Disorders: Raynaud's phenomenon

7 DRUG INTERACTIONS

7.1 Clinically Important Drug Interactions

Table 6 presents clinically important drug interactions with methylphenidate hydrochloride extended-release tablets.

Table 6: Drugs Having Clinically Important Interactions with Methylphenidate Hydrochloride Extended-release Tablets

Monoamine Oxidase Inhibitors (MAOI)	
Clinical Impact:	Concomitant use of MAOIs and CNS stimulants 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:	Do not administer methylphenidate hydrochloride extended-release tablets concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment.
Antihypertensive Drugs	
Clinical Impact:	Methylphenidate hydrochloride extended-release tablets 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.
Halogenated Anesthetics	
Clinical Impact:	Concomitant use of halogenated anesthetics and methylphenidate hydrochloride extended-release tablets may increase the risk of sudden blood pressure and heart rate increase during surgery.
Intervention:	Avoid use of methylphenidate hydrochloride extended-release tablets in patients being treated with anesthetics on the day of surgery.
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 extended-release tablets, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for ADHD Medications at 1-866-961-2388.

Risk Summary

Published studies and post-marketing 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 are risks to the fetus associated with the use of central nervous system (CNS) stimulants during pregnancy *(*see *Clinical Considerations).*

No effects on morphological development were observed in development studies with oral administration of methylphenidate to pregnant rats at doses up to 4 times the maximum recommended human dose (MRHD) of 72 mg/day

given to adults on a mg/m^2 basis. However, malformations were observed in rabbits at a dose 54 times the MRHD given to adults.

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 extended-release 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 development studies conducted in rats and rabbits, methylphenidate was administered at doses up to 30 and 200 mg/kg/day, respectively. Methylphenidate has been shown to cause malformations in rabbits when given in doses of 200 mg/kg/day, which is approximately 54 times the MRHD on a mg/m^2 basis, respectively. A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 4-fold the MRHD on a mg/m^2 basis.

8.2 Lactation

Risk Summary

Limited published literature, based on breast milk sampling from five 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. However, long-term neurodevelopmental effects on infants from CNS stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for methylphenidate hydrochloride extended-release tablets and any potential adverse effects on the breastfed infant from methylphenidate hydrochloride extended-release tablets or from the underlying maternal condition.

Clinical Considerations

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

8.4 Pediatric Use

The safety and effectiveness of methylphenidate hydrochloride extended-release tablets have not been established in pediatric patients below the age of 6 years.

In studies evaluating extended-release methylphenidate products, patients 4 to <6 years of age had higher systemic methylphenidate exposures than those observed in older pediatric patients at the same dosage. Pediatric patients 4 to <6 years of age also had a higher incidence of adverse reactions, including weight loss.

The safety and effectiveness of methylphenidate hydrochloride extended-release tablets for the treatment of ADHD have been established in pediatric patients 6 to 17 years.

Long Term Suppression of Growth

Growth should be monitored during treatment with stimulants, including methylphenidate hydrochloride extended-release tablets. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.7) and Adverse Reactions (6.1)]*.

Juvenile Animal Toxicity Data

In the 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 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 4 times the MRHD of 54 mg/day given to children on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was observed in females exposed to the highest dose (9 times the MRHD given to children on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (equal to the MRHD given to children on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use

Methylphenidate hydrochloride extended-release tablets have not been studied in patients greater than 65 years of age.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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

9.2 Abuse

Methylphenidate hydrochloride extended-release tablets have a high potential for abuse and misuse which can lead to the development of a substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*. Methylphenidate hydrochloride extended-release tablets can be diverted for non-medical use into illicit channels or distribution.

Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of methylphenidate may cause increased heart rate, respiratory rate, or blood pressure; 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 with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including methylphenidate hydrochloride extended-release tablets, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration such as snorting or injection.

In two placebo-controlled human abuse potential studies, single oral doses of another formulation of methylphenidate hydrochloride extended-release tablets were compared to single oral doses of immediate-release methylphenidate (IR MPH) and placebo in subjects with a history of recreational stimulant use to assess relative abuse potential. For the purpose of this assessment, the response for each of the subjective measures was defined as the maximum effect within the first 8 hours after dose administration.

In one study (n=40), both the other formulation of methylphenidate hydrochloride extended-release tablets (108 mg, which is 1.5 times the maximum recommended dosage of methylphenidate hydrochloride extended-release tablets) and 60 mg IR MPH compared to placebo produced statistically significantly greater responses on the five subjective measures suggestive of abuse potential. In comparisons between the two active treatments, however, the other formulation of methylphenidate hydrochloride extended-release tablets (108 mg) produced variable responses on positive subjective measures that were either statistically indistinguishable from (Abuse Potential, Drug Liking, Amphetamine, and Morphine Benzedrine Group [Euphoria]) or statistically less than (Stimulation – Euphoria) responses produced by 60 mg IR MPH.

In another study (n=49), both doses of another formulation of methylphenidate hydrochloride extended-release tablets (54 mg and 108 mg) and both doses of IR MPH (50 mg and 90 mg) produced statistically significantly greater responses compared to placebo on the two primary scales used in the study (Drug Liking, Euphoria). When doses of the other methylphenidate hydrochloride extended-release tablets (54 mg and 108 mg) were compared to IR MPH (50 mg and 90 mg), respectively, methylphenidate hydrochloride extended-release tablets produced statistically significantly lower subjective responses on these two scales than IR MPH. Methylphenidate hydrochloride extended-release tablets (108 mg)

produced responses that were statistically indistinguishable from the responses on these two scales produced by IR MPH (50 mg). Differences in subjective responses to the respective doses should be considered in the context that only 18% of the total amount of methylphenidate in methylphenidate hydrochloride extended-release tablets is available for immediate release from the drug overcoat.

Although these findings reveal a relatively lower response to another formulation of methylphenidate hydrochloride extended-release tablets on subjective measures suggestive of abuse potential compared to IR MPH at roughly equivalent total MPH doses, the relevance of these findings to the abuse potential of methylphenidate hydrochloride extended-release tablets in the community is unknown.

9.3 Dependence

Physical Dependence

Methylphenidate hydrochloride extended-release tablets may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal signs and symptoms after abrupt discontinuation or dose reduction following prolonged use of CNS stimulants including methylphenidate hydrochloride extended-release tablets include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

Tolerance

Methylphenidate hydrochloride extended-release tablets may produce tolerance. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained by a lower dose).

10 OVERDOSAGE

Clinical Effects of Overdose

Overdose of CNS stimulants is characterized by the following sympathomimetic effects:

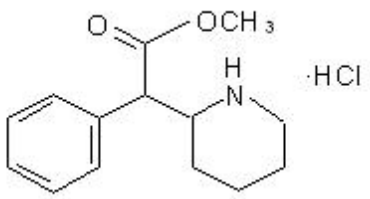
- Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden cardiac death. Takotsubo cardiomyopathy may develop.
- CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin syndrome, seizures, cerebral vascular accidents, and coma may occur.
- Life-threatening hyperthermia (temperatures greater than 104°F) and rhabdomyolysis may develop.

Overdose Management

Consider the possibility of multiple drug ingestion. The pharmacokinetic profile of methylphenidate hydrochloride tablets should be considered when treating patients with overdose. Because methylphenidate has a large volume of distribution and is rapidly metabolized, dialysis is not useful. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

Methylphenidate hydrochloride extended-release tablets contain methylphenidate a CNS stimulant, present as methylphenidate hydrochloride salt. Chemically, methylphenidate hydrochloride is d,l (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is $C_{14}H_{19}NO_2$•HCl. Its structural formula is:



Methylphenidate hydrochloride is a white, odorless 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. It has a pKa of 8.71 (at 21.5°C). Its molecular weight is 269.77.

Methylphenidate hydrochloride extended-release tablets are for oral administration and is available in the following strengths: 18 mg, 27 mg, 36 mg, 45 mg, 54 mg, 63 mg, and 72 mg containing methylphenidate hydrochloride (equivalent to 15.6 mg, 23.4 mg, 31.1 mg, 38.9 mg, 46.7 mg, 54.5 mg, and 62.3 mg methylphenidate respectively).

Methylphenidate hydrochloride extended-release tablets contain the following inactive ingredients: cellulose acetate, colloidal silicon dioxide, ferrosoferric oxide, hypromellose, iron oxide black, lactose monohydrate, magnesium stearate, phosphoric acid, polyethylene glycol, polyethylene oxide, sodium chloride, succinic acid, titanium dioxide, triacetin.

Methylphenidate hydrochloride extended-release tablets also contain the following color additives:

27 mg: FD&C Yellow #6 Aluminum Lake, FD&C Blue #2 Aluminum Lake, FD&C Red #40 Aluminum Lake

45 mg: FD&C Red #40 Aluminum Lake

54 mg: FD&C Yellow #6 Aluminum Lake, FD&C Red #40 Aluminum Lake, FD&C Blue #2 Aluminum Lake

18 and 63 mg: iron oxide red, iron oxide yellow

72 mg: FD&C Blue #1 Aluminum Lake

System Components and Performance

Methylphenidate hydrochloride extended-release tablets use osmotic pressure to deliver methylphenidate hydrochloride at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active bilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within one hour, providing an initial dose of methylphenidate. Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The membrane controls the rate at which water enters the tablet core, which in turn controls drug delivery. Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug-concentration gradient incorporated into the two drug layers of core of methylphenidate hydrochloride extended-release tablets. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell along with insoluble core components. It is possible that methylphenidate hydrochloride extended-release tablets may be visible on abdominal x-rays under certain circumstances, especially when digital enhancing techniques are utilized.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate HCl is a CNS stimulant. The mode of therapeutic action in ADHD is not known.

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprised of the d- and l-threo entantiomers. The d-threo enantiomer is more pharmacologically active than the l-threo enantiomer. Methylphenidate blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

12.3 Pharmacokinetics

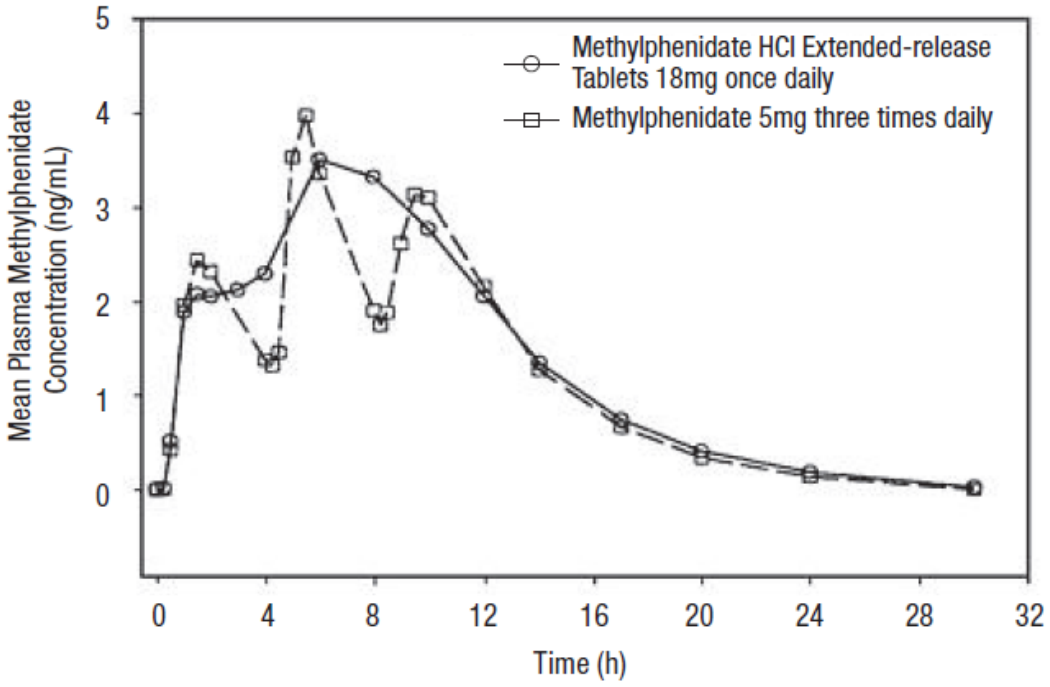
In a relative bioavailability study in healthy adults under fasted conditions, plasma exposures of 72 mg methylphenidate hydrochloride extended-release tablets and 72 mg (2 x 36 mg) methylphenidate extended-release tablets were compared. The peak plasma concentration (C_{max}) of 72 mg methylphenidate hydrochloride extended-release tablets and 72 mg (2 x 36 mg) methylphenidate extended-release tablets is 19.7 ng/mL and 19.3 ng/mL, respectively. The area under the plasma concentration-time curve ($AUC_{0\text{-}inf}$) of 72 mg methylphenidate hydrochloride extended-release tablets and 72 mg (2 x 36 mg) methylphenidate extended-release tablets is 206.1 ng·h/mL and 200.9 ng·h/mL, respectively.

Absorption

Methylphenidate is readily absorbed. Following oral administration of methylphenidate hydrochloride extended-release tablets plasma methylphenidate concentrations increase rapidly, reaching an initial maximum at about 1.5 hour, followed by gradual ascending concentrations over the next 5 to 6 hours, after which a gradual decrease begins. Mean time to reach peak plasma concentrations of methylphenidate hydrochloride extended-release tablets occurs at 5.5 hours.

Methylphenidate hydrochloride extended-release tablets once daily minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily. Figure 1 displays mean plasma exposures of methylphenidate hydrochloride extended-release tablets once daily and methylphenidate three times daily (administered every 4 hours) in adults.

Figure 1: Mean Methylphenidate Plasma Concentration-Time Profiles



The mean single-dose pharmacokinetic parameters in 36 healthy adults following the administration of methylphenidate hydrochloride extended-release tablets 18 mg once daily and methylphenidate 5 mg three times daily are summarized in Table 7.

Table 7: Methylphenidate Pharmacokinetic Parameters (Mean ± SD) After Single Dose in Healthy Adults

Parameters	**Methylphenidate Hydrochloride Extended-release Tablets (18 mg once daily) (n=36)**	**Methylphenidate (5 mg three times daily) (n=35)**
C_{max} (ng/mL)	3.7 ± 1.0	4.2 ± 1.0
T_{max} (h)	6.8 ± 1.8	6.5 ± 1.8
AUC_{inf} (ng·h/mL)	41.8 ± 13.9	38.0 ± 11.0
$t_{½}$ (h)	3.5 ± 0.4	3.0 ± 0.5

The pharmacokinetics of methylphenidate hydrochloride extended-release tablets were evaluated in healthy adults following single- and multiple-dose administration (steady state) of doses up to 144 mg per day (2 times the maximum recommended daily dosage of methylphenidate hydrochloride extended-release tablets). The mean half-life was about 3.6 hours. No differences in the pharmacokinetics of methylphenidate hydrochloride extended-release tablets were noted following single and repeated once-daily dosing, indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated once-daily dosing are similar to those following the first dose of methylphenidate hydrochloride extended-release tablets in a dose range of 18 mg to 144 mg.

Effect of Food

There were no differences in either the pharmacokinetics or the pharmacodynamic performance of methylphenidate hydrochloride extended-release tablets when administered after a high-fat breakfast. There is no evidence of dose dumping in the presence or absence of food.

Effect of Alcohol

In-vitro studies were conducted to explore the effect of alcohol on the release characteristics of methylphenidate from methylphenidate hydrochloride extended-release tablets. At alcohol concentrations up to 40%, there was no increased release of methylphenidate in the first two hours.

Dose Proportionality

Following administration methylphenidate hydrochloride extended-release tablets in single doses of 18 mg, 36 mg, and 54 mg per day to healthy adults, C_{max} and $AUC_{(0–inf)}$ of d-methylphenidate were proportional to dose, whereas l-methylphenidate C_{max} and $AUC_{(0–inf)}$ increased disproportionately with respect to dose. Following administration of methylphenidate hydrochloride extended-release tablets, plasma concentrations of the l-isomer were approximately 1/40 the plasma concentrations of the d-isomer.

In healthy adults, single and multiple dosing of once-daily methylphenidate hydrochloride extended-release tablets doses from 54 mg to 144 mg per day resulted in linear and dose-proportional increases in C_{max} and AUC_{inf} for total methylphenidate (MPH) and its major metabolite, α-phenyl-piperidine acetic acid (PPAA). There was no time dependency in the pharmacokinetics of methylphenidate. The ratio of metabolite (PPAA) to parent drug (MPH) was constant across doses from 54 mg to 144 mg per day, both after single dose and upon multiple dosing.

In a multiple-dose study in ADHD with pediatric patients 13 to 16 years administered their prescribed dose (18 mg to 72 mg per day) of methylphenidate hydrochloride extended-release tablets, mean C_{max} and AUC_{TAU} of d- and total methylphenidate increased proportionally with respect to dose.

Distribution

Plasma methylphenidate concentrations in adults and pediatric patients 13 to 17 years decline biexponentially following oral administration. The half-life of methylphenidate in adults and adolescents following oral administration of methylphenidate hydrochloride extended-release tablets was approximately 3.5 hours.

Elimination

Metabolism

In humans, methylphenidate is metabolized primarily by de-esterification to PPAA, which has little or no pharmacologic activity. In adults the metabolism of methylphenidate hydrochloride extended-release tablets once daily as evaluated by metabolism to PPAA is similar to that of methylphenidate three times daily. The metabolism of single and repeated once-daily doses of methylphenidate hydrochloride extended-release tablets is similar.

Excretion

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose.

Specific Populations

Male and Female Patients

In healthy adults, the mean dose-adjusted $AUC_{(0–inf)}$ values for methylphenidate hydrochloride extended-release tablets were 36.7 ng·h/mL in men and 37.1 ng·h/mL in women, with no differences noted between the two groups.

Racial or Ethnic Groups

In adults receiving methylphenidate hydrochloride extended-release tablets, dose-adjusted $AUC_{(0–inf)}$ was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Pediatric Patients

Increase in age resulted in increased apparent oral clearance (CL/F) (58% increase in pediatric patients 13 to 17 years compared to pediatric patients 6 to 12 years). Some of these differences could be explained by body-weight differences

among these populations. This suggests that subjects with higher body weight may have lower exposures of total methylphenidate at similar doses.

The pharmacokinetics of methylphenidate hydrochloride extended-release tablets have not been studied in pediatric patients less than 6 years of age.

Patients with Renal Impairment

There is no experience with the use of methylphenidate hydrochloride extended-release tablets in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPAA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of methylphenidate hydrochloride extended-release tablets.

Patients with Hepatic Impairment

There is no experience with the use of methylphenidate hydrochloride extended-release tablets in patients with hepatic insufficiency.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

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 4 times the MRHD of methylphenidate hydrochloride extended-release tablets on a 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 6 times the MRHD of methylphenidate hydrochloride extended-release tablets on a 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.

Mutagenesis

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or 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 cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus assay.

Impairment of Fertility

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 11-fold the MRHD of methylphenidate hydrochloride extended-release tablets on a mg/m^2 basis, respectively.

14 CLINICAL STUDIES

The efficacy of methylphenidate hydrochloride extended-release tablets for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients (6 to 17 years) and adult patients is based upon adequate and well-controlled studies of another formulation of methylphenidate hydrochloride extended-release tablets (referred to as "methylphenidate hydrochloride extended-release tablets" in the section below). The results of these adequate and well-controlled studies are presented below.

Methylphenidate hydrochloride extended-release tablets was demonstrated to be effective in the treatment of Attention

Deficit Hyperactivity Disorder (ADHD) in four randomized, double-blind, placebo-controlled studies in pediatric patients 6 to 17 years and two double-blind placebo-controlled studies in adults who met the Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD.

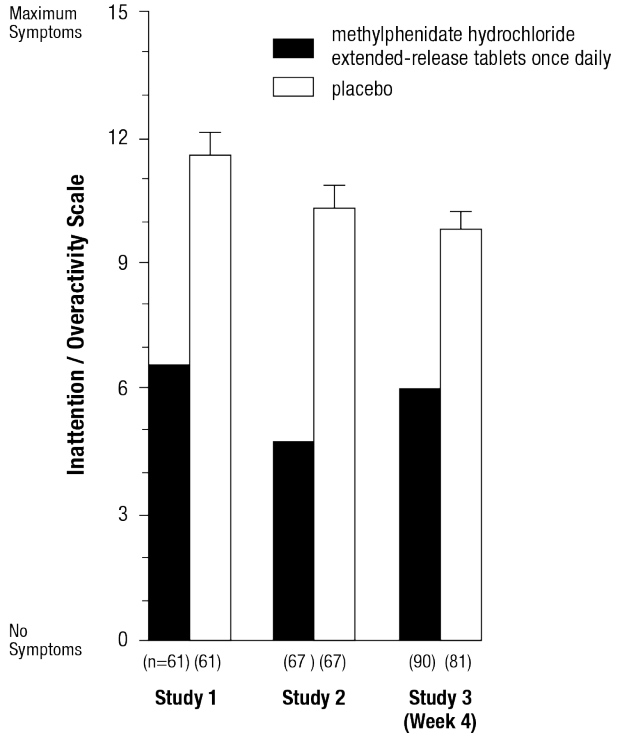
Pediatric Patients 6 to 12 Years

Three double-blind, active- and placebo-controlled studies were conducted in 416 pediatric patients 6 to 12 years. The controlled studies compared methylphenidate hydrochloride extended-release tablets given once daily (18 mg, 36 mg, or 54 mg), methylphenidate given three times daily over 12 hours (15 mg, 30 mg, or 45 mg total daily dose), and placebo in two single-center, 3-week crossover studies (Studies 1 and 2) and in a multicenter, 4-week, parallel-group comparison (Study 3). The primary comparison of interest in all three trials was methylphenidate hydrochloride extended-release tablets versus placebo.

Symptoms of ADHD were evaluated by community schoolteachers using the Inattention/Overactivity with Aggression (IOWA) Conners scale. Statistically significant reduction in the Inattention/Overactivity subscale versus placebo was shown consistently across all three controlled studies for methylphenidate hydrochloride extended-release tablets. Studies 1 and 2 involved a 3-way crossover of 1 week per treatment arm. Study 3 involved 4 weeks of parallel-group treatments with a Last Observation Carried Forward analysis at Week 4.

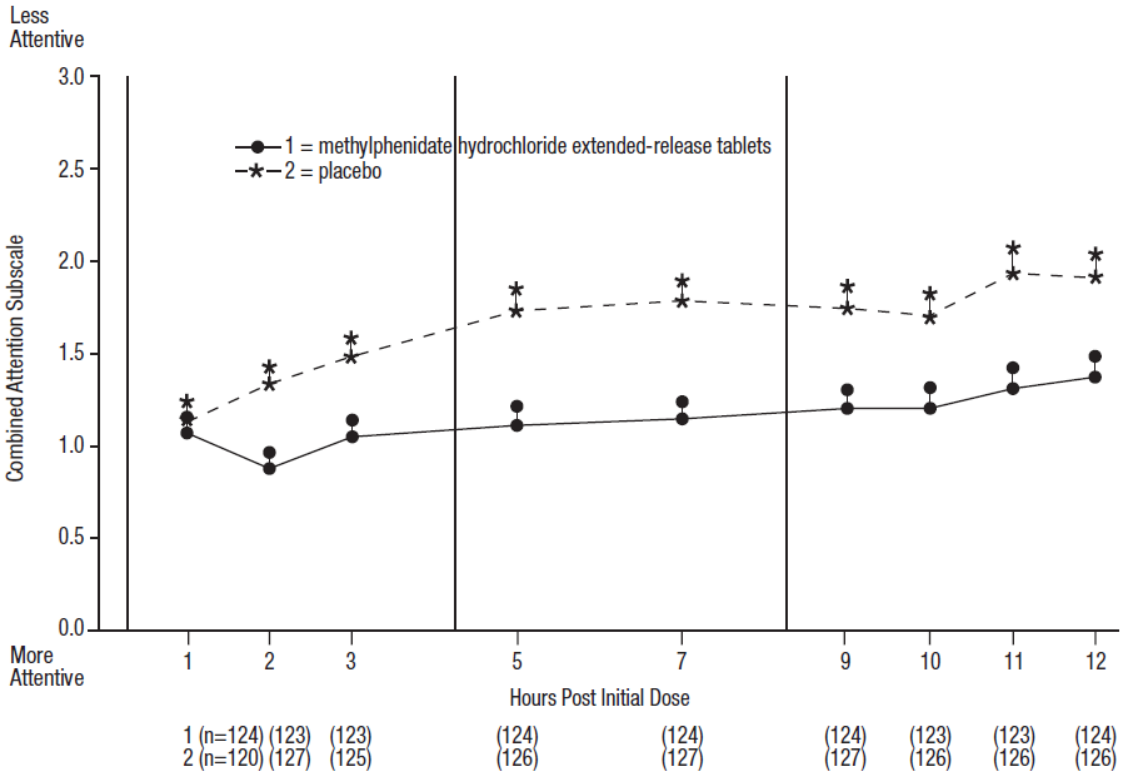
The scores for methylphenidate hydrochloride extended-release tablets and placebo for the three studies are presented in Figure 2. Error bars represent the mean plus standard error of the mean.

Figure 2: Mean Community School Teacher IOWA Conners Inattention/Overactivity Scores with Methylphenidate Hydrochloride Extended-Release Tablets Once Daily (18 mg, 36 mg, or 54 mg) and Placebo (Studies 1, 2, and 3)



In Studies 1 and 2, symptoms of ADHD were evaluated by laboratory schoolteachers using the Swanson, Kotkin, Agler, M-Fynn, and Pelham (SKAMP) laboratory school rating scale. The combined results from these two studies demonstrated statistically significant improvements in attention and behavior in patients treated with methylphenidate hydrochloride extended-release tablets versus placebo that were maintained through 12 hours after dosing. Figure 3 presents the laboratory schoolteacher SKAMP ratings for methylphenidate hydrochloride extended-release tablets and placebo.

Figure 3: Laboratory School Teacher SKAMP Ratings: Mean (SEM) of Combined Attention (Studies 1 and 2)



Note: Mean and mean plus standard error of mean shown

Pediatric Patients 13 to 17 years

In a randomized, double-blind, multicenter, placebo-controlled trial (Study 4) involving 177 patients, methylphenidate hydrochloride extended-release tablets was demonstrated to be effective in the treatment of ADHD in pediatric patients aged 13 to 18 years at doses up to 72 mg once daily (1.4 mg/kg/day). Of 220 patients who entered an open 4-week titration phase, 177 were titrated to an individualized dose (maximum of 72 mg once daily) based on meeting specific improvement criteria on the ADHD Rating Scale and the Global Assessment of Effectiveness with acceptable tolerability. Patients who met these criteria were then randomized to receive either their individualized dose of methylphenidate hydrochloride extended-release tablets (18 mg to 72 mg once daily, n=87) or placebo (n=90) during a two-week double-blind phase. At the end of this phase, mean scores for the investigator rating on the ADHD Rating Scale demonstrated that methylphenidate hydrochloride extended-release tablets was statistically significantly superior to placebo.

Adults

Two double-blind, placebo-controlled studies were conducted in 627 adults aged 18 to 65 years. The controlled studies compared methylphenidate hydrochloride extended-release tablets administered once daily and placebo in a multicenter, parallel-group, 7-week dose-titration study (Study 5) (36 mg to 108 mg once daily) and in a multicenter, parallel-group, 5-week, fixed-dose study (Study 6) (18 mg, 36 mg, and 72 mg once daily).

Study 5 demonstrated the effectiveness of methylphenidate hydrochloride extended-release tablets in the treatment of ADHD in adults aged 18 to 65 years at doses from 36 mg once daily to 108 mg once daily based on the change from baseline to final study visit on the Adult ADHD Investigator Rating Scale (AISRS). Of 226 patients who entered the 7-week trial, 110 were randomized to methylphenidate hydrochloride extended-release tablets and 116 were randomized to placebo. Treatment was initiated at 36 mg once daily and patients continued with incremental increases of 18 mg once daily (36 mg to 108 mg once daily) based on meeting specific improvement criteria with acceptable tolerability. At the final study visit, mean change scores (LS Mean, SEM) for the investigator rating on the AISRS demonstrated methylphenidate hydrochloride extended-release tablets was statistically significantly superior to placebo.

Study 6 was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-response study (5-week duration) with 3 fixed-dose groups (18 mg, 36 mg, and 72 mg). Patients were randomized to receive methylphenidate

hydrochloride extended-release tablets administered at doses of 18 mg (n=101), 36 mg (n=102), 72 mg once daily (n=102), or placebo (n=96). All three doses of methylphenidate hydrochloride extended-release tablets were statistically significantly more effective than placebo in improving CAARS (Conners' Adult ADHD Rating Scale) total scores at double-blind end point in adult subjects with ADHD.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Methylphenidate hydrochloride extended-release tablets are available as:

- 18 mg yellow tablets with “TL706” imprinted in black ink
    - NDC 13811-706-10 in 100-count bottle
- 27 mg gray tablets with “TL707” imprinted in black ink
    - NDC 13811-707-10 in 100-count bottle
- 36 mg white tablets with “TL708” imprinted in black ink
    - NDC 13811-708-10 in 100-count bottle
- 45 mg pink tablets with “TL711” imprinted in black ink
    - NDC 13811-711-30 in 30-count bottle
- 54 mg pink tablets with “TL709” imprinted in black ink
    - NDC 13811-709-10 in 100-count bottle
- 63 mg orange tablets with “TL700” imprinted in black ink
    - NDC 13811-700-30 in 30-count bottle
- 72 mg blue tablets with “TL710” imprinted in black ink
    - NDC 13811-710-30 in 30-count bottle

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from humidity.

17 PATIENT COUNSELING INFORMATION

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

Abuse, Misuse, and Addiction

Educate patients and their families about the risks of abuse, misuse, and addiction of methylphenidate hydrochloride extended-release tablets, which can lead to overdose and death, and proper disposal of any unused drug *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2), and Overdosage (10)]*. Advise patients to store methylphenidate hydrochloride extended-release tablets in a safe place, preferably locked, and instruct patients to not give methylphenidate hydrochloride extended-release tablets to anyone else.

Administration Instructions

Instruct patients to swallow methylphenidate hydrochloride extended-release tablets whole with the aid of liquids, and not to chew, divide, or crush the tablets. Advise patients that the medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; advise patients not to be concerned if they occasionally notice in their stool something that looks like a tablet *[see Dosage and Administration (2.2), Warnings and Precautions (5.8)]*.

Risks to Patients with Serious Cardiac Disease

Advise patients that there are potential risks to patients with serious cardiac disease, including sudden death with methylphenidate hydrochloride extended-release tablets use. Instruct patients to contact a healthcare provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease *[see Warnings and Precautions (5.2)]*.

Increased Blood Pressure and Heart Rate

Advise patients and their caregivers that methylphenidate hydrochloride extended-release tablets can cause elevations of their blood pressure and pulse rate *[see Warnings and Precautions (5.3)]*.

Psychiatric Adverse Reactions

Advise patients and their caregivers that methylphenidate hydrochloride extended-release tablets, at recommended doses, can cause psychotic or manic symptoms, even in patients without prior history of psychotic symptoms or mania *[see Warnings and Precautions (5.4)]*.

Priapism

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

Circulation Problems in Fingers and Toes [Peripheral Vasculopathy, including Raynaud's Phenomenon] *[see Warnings and Precautions (5.6)]*.

- Instruct patients beginning treatment with methylphenidate hydrochloride extended-release tablets about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change color from pale, to blue, to red.
- Instruct patients to report to their healthcare provider any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes.
- Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking methylphenidate hydrochloride extended-release tablets.
- Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

Long-Term Suppression of Growth in Pediatric Patients

Advise patients, families and caregivers that methylphenidate hydrochloride extended-release tablets may cause slowing of growth and weight loss *[see Warnings and Precautions (5.7)]*.

Increased Intraocular Pressure (IOP) and Glaucoma

Advise patients that IOP and glaucoma may occur during treatment with methylphenidate hydrochloride extended-release tablets *[see Warnings and Precautions (5.10)]*.

Motor and Verbal Tics, and Worsening of Tourette's Syndrome

Advise patients that motor and verbal tics and worsening of Tourette's Syndrome may occur during treatment with methylphenidate hydrochloride extended-release tablets. Instruct patients to notify their healthcare provider if emergence of new tics or worsening of tics or Tourette's syndrome occurs *[see Warnings and Precautions (5.11)]*.

Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to methylphenidate hydrochloride extended-release tablets during pregnancy *[see Use in Specific Populations (8.1)]*.

Manufactured for:

Trigen Laboratories, LLC
Alpharetta, GA 30005
1-800-444-5164
www.trigenlab.com

200320-4

Patent numbers:
US 9,855,258
US 9,827,234
US 9,707,217
US 10,265,308
US 10,695,336

MEDICATION GUIDE
Methylphenidate hydrochloride extended-release tablets
(METH-il-FEN-i-date)
for oral use, CII

What is the most important information I should know about methylphenidate hydrochloride extended-release tablets?

Methylphenidate hydrochloride extended-release tablets may cause serious side effects, including:

- **Abuse, misuse, and addiction.** Methylphenidate hydrochloride extended-release tablets have a high chance for abuse and misuse and may lead to substance use problems, including addiction. Misuse and abuse of methylphenidate hydrochloride extended-release tablets, other methylphenidate containing medicines, and amphetamine containing medicines, can lead to overdose and death. The risk of overdose and death is increased with higher doses of methylphenidate hydrochloride extended-release tablets or when it is used in ways that are not approved, such as snorting or injection.
  - Your healthcare provider should check you or your child's risk for abuse, misuse, and addiction before starting treatment with methylphenidate hydrochloride extended-release tablets and will monitor you or your child during treatment.
  - Methylphenidate hydrochloride extended-release tablets may lead to physical dependence after prolonged use, even if taken as directed by your healthcare provider.
  - Do not give methylphenidate hydrochloride extended-release tablets to anyone else. See "**What are methylphenidate hydrochloride extended-release tablets?**" for more information.
  - Keep methylphenidate hydrochloride extended-release tablets in a safe place and properly dispose of any unused medicine. See "**How should I store methylphenidate hydrochloride extended-release tablets?**" for more information.
  - Tell your healthcare provider if you or your child have ever abused or been dependent on alcohol, prescription medicines, or street drugs.
- **Risks for people with serious heart disease.** Sudden death has happened in people who have heart defects or other serious heart disease.

  Your healthcare provider should check you or your child carefully for heart problems before starting treatment with methylphenidate hydrochloride extended-release tablets. Tell your healthcare provider if you or your child have any heart problems, heart disease, or heart defects.

  Call your healthcare provider or go to the nearest hospital emergency room right away if you or your child have any signs of heart problems such as chest pain, shortness of breath, or fainting during treatment with methylphenidate hydrochloride extended-release tablets.
- **Increased blood pressure and heart rate.**

  Your healthcare provider should check your or your child's blood pressure and heart rate regularly during treatment with methylphenidate hydrochloride extended-release tablets.
- **Mental (psychiatric) problems, including:**
  - new or worse behavior and thought problems
  - new or worse bipolar illness

- new psychotic symptoms (such as hearing voices, or seeing or believing things that are not real) or new manic symptoms

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

Call your healthcare provider right away if you or your child have any new or worsening mental symptoms or problems during treatment with methylphenidate hydrochloride extended-release tablets, especially hearing voices, seeing or believing things that are not real, or new manic symptoms.

What are methylphenidate hydrochloride extended-release tablets?

Methylphenidate hydrochloride extended-release tablets are a central nervous system (CNS) stimulant prescription medicine used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults less than 65 years of age and children 6 years of age and older**.** Methylphenidate hydrochloride extended-release tablets may help increase attention and decrease impulsiveness and hyperactivity in people with ADHD.

Methylphenidate hydrochloride extended-release tablets are not recommended for use in children under 6 years of age with ADHD.

Methylphenidate hydrochloride extended-release tablets have not been studied in adults older than 65 years of age.

Methylphenidate hydrochloride extended-release tablets are a federally controlled substance (CII) because it contains methylphenidate that can be a target for people who abuse prescription medicines or street drugs. Keep methylphenidate hydrochloride extended-release tablets in a safe place to protect it from theft. Never give your methylphenidate hydrochloride extended-release tablets to anyone else because it may cause death or harm them. Selling or giving away methylphenidate hydrochloride extended-release tablets may harm others and is against the law.

Do not take methylphenidate hydrochloride extended-release tablets if: you or your child are:

- allergic to methylphenidate or any of the ingredients in methylphenidate hydrochloride extended-release tablets. See the end of this Medication Guide for a complete list of ingredients in methylphenidate hydrochloride extended-release tablets.
- taking, or have stopped taking within the past 14 days, a medicine called a monoamine oxidase inhibitor (MAOI).

Before taking methylphenidate hydrochloride extended-release tablets tell your healthcare provider about all your medical conditions, including if you or your child:

- have heart problems, heart disease, heart defects, or high blood pressure
- have mental problems including psychosis, mania, bipolar illness, or depression, or a family history of suicide, bipolar illness, or depression
- have circulation problems in fingers and toes
- have eye problems, including increased pressure in your eye, glaucoma, or problems with your close-up vision (farsightedness)
- have or had repeated movements or sounds (tics) or Tourette's syndrome, or have a family history of tics or Tourette's syndrome
- are pregnant or plan to become pregnant. It is not known if methylphenidate hydrochloride extended-release tablets will harm the unborn baby.
  - **Pregnancy Exposure Registry:** There is a pregnancy registry for women who are exposed to methylphenidate hydrochloride extended-release tablets during pregnancy. The purpose of the registry is to collect information about the health of women exposed to methylphenidate hydrochloride extended-release tablets and their baby. If you or your child becomes pregnant during treatment with methylphenidate hydrochloride extended-release tablets, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychostimulants at 1-866-961-2388.
- are breastfeeding or plan to breastfeed. Methylphenidate hydrochloride extended-release tablets passes into breast milk. Talk to your healthcare provider about the best way to feed the baby during treatment with methylphenidate hydrochloride extended-release tablets.

Tell your healthcare provider about all of the medicines that you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Methylphenidate hydrochloride extended-release tablets and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be changed during treatment with methylphenidate hydrochloride extended-release tablets. Your healthcare provider will decide whether methylphenidate hydrochloride extended-release tablets can be taken with other medicines.

Especially tell your healthcare provider if you or your child takes:

blood pressure medicines (anti-hypertensive)

Know the medicines that you take or your child take. Keep a list of your medicines with you to show your healthcare provider and pharmacist. **Do not start any new medicine during treatment with methylphenidate hydrochloride extended-release tablets without first talking to your healthcare provider.**

How should methylphenidate hydrochloride extended-release tablets be taken?

- Take methylphenidate hydrochloride extended-release tablets exactly as prescribed by your healthcare provider.
- Your healthcare provider may change the dose or tell you to stop taking methylphenidate hydrochloride extended-release tablets if needed.
- Take methylphenidate hydrochloride extended-release tablets 1 time each day in the morning with or without food.
- Swallow methylphenidate hydrochloride extended-release tablets whole with water or other liquids. Do not chew, crush, or divide the tablets. Tell your healthcare provider if you or your child cannot swallow methylphenidate hydrochloride extended-release tablets whole. A different medicine may need to be prescribed.
- Methylphenidate hydrochloride extended-release tablets does not dissolve completely in the body after all the medicine has been released. You or your child may sometimes notice the empty tablet in a bowel movement. This is normal.

If you or your child take too much methylphenidate hydrochloride extended-release tablets, call your healthcare provider or Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of methylphenidate hydrochloride extended-release tablets?

Methylphenidate hydrochloride extended-release tablets may cause serious side effects, including:

- See **"What is the most important information I should know about methylphenidate hydrochloride extended-release tablets?"**
- **Painful and prolonged erections (priapism).** Priapism that may require surgery has happened in males who take products that contain methylphenidate. **If you or your child develop priapism, get medical help right away.**
- **Circulation problems in fingers and toes (peripheral vasculopathy, including Raynaud's phenomenon):** Signs and symptoms may include:
  - fingers or toes may feel numb, cool, painful
  - fingers or toes may change color from pale, to blue, to red

  Tell your healthcare provider if you or your child have numbness, pain, skin color change, or sensitivity to temperature in your fingers or toes, or if you or your child have any signs of unexplained wounds appearing on fingers or toes during treatment with methylphenidate hydrochloride extended-release tablets.
- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with methylphenidate hydrochloride extended-release tablets. Methylphenidate hydrochloride extended-release tablets treatment may be stopped if your child is not growing or gaining weight.
- **Possible blockage of the intestine.** Because the methylphenidate hydrochloride extended-release tablet does not change in shape in the intestines (GI tract), methylphenidate hydrochloride extended-release tablets should not be taken by people with severe intestinal problems (preexisting severe gastrointestinal narrowing).
- **Eye problems (increased pressure in the eye and glaucoma).** Call your healthcare provider right away if you or your child develop changes in your vision or eye pain, swelling, or redness.
- **New or worsening tics or worsening Tourette's syndrome.** Tell your healthcare provider if you or your child get any new or worsening tics or worsening Tourette's syndrome during treatment with methylphenidate hydrochloride extended-release tablets.

The most common side effects of methylphenidate hydrochloride extended-release tablets in adults include:

- decreased appetite
- dry mouth
- trouble sleeping (insomnia)
- dizziness
- irritability
- headache
- nausea
- anxiety
- weight loss
- increased sweating

The most common side effects of methylphenidate hydrochloride extended-release tablets in children 6 to 17 years of age was stomach pain.

These are not all the possible side effects of methylphenidate hydrochloride extended-release tablets.

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

How should I store methylphenidate hydrochloride extended-release tablets?

- Store methylphenidate hydrochloride extended-release tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Store methylphenidate hydrochloride extended-release tablets in a safe place, like a locked cabinet. Protect from light and moisture.
- Dispose of remaining, unused, or expired methylphenidate hydrochloride extended-release tablets by a medicine take-back program at a U.S. Drug Enforcement Administration (DEA) authorized collection site. If no take-back program or DEA authorized collector is available, mix methylphenidate hydrochloride extended-release tablets with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away methylphenidate hydrochloride extended-release tablets in the household trash. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Keep methylphenidate hydrochloride extended-release tablets and all medicines out of the reach of children.

General information about the safe and effective use of methylphenidate hydrochloride extended-release tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use methylphenidate hydrochloride extended-release tablets for a condition for which it was not prescribed. Do not give methylphenidate hydrochloride extended-release tablets to other people, even if they have the same symptoms that you have. It may harm them and it is against the law. You can ask your healthcare provider or pharmacist for information about methylphenidate hydrochloride extended-release tablets that is written for healthcare professionals.

What are the ingredients in methylphenidate hydrochloride extended-release tablets?

Active Ingredient: methylphenidate hydrochloride

Inactive Ingredients: cellulose acetate, colloidal silicon dioxide, ferrosoferric oxide, hypromellose, iron oxide black, lactose monohydrate, magnesium stearate, phosphoric acid, polyethylene glycol, polyethylene oxide, sodium chloride, succinic acid, titanium dioxide, and triacetin.

27 mg tablets contain: FD&C Yellow #6 Aluminum Lake, FD&C Blue #2 Aluminum Lake, FD&C Red #40 Aluminum Lake

45 mg tablets contain: FD&C Red #40 Aluminum Lake

54 mg tablets contain: FD&C Yellow #6 Aluminum Lake, FD&C Red #40 Aluminum Lake, FD&C Blue #2 Aluminum Lake

18 and 63 mg tablets contain: iron oxide red, iron oxide yellow

72 mg tablets contain: FD&C Blue #1 Aluminum Lake

Manufactured for:

Trigen Laboratories, LLC

Alpharetta, GA 30005

TRIGEN LABORATORIES

For more information, go to www.trigenlab.com or call 1-800-444-5164

200320-4

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 09/2025

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use methylphenidate hydrochloride extended-release tablets USP safely and effectively. See full prescribing information for METHYLPHENIDATE hydrochloride extended-release tablets USP.

METHYLPHENIDATE hydrochloride extended-release tablets USP, for oral use, CII

Initial U.S. Approval: 2000

WARNING: ABUSE, MISUSE, AND ADDICTION
See full prescribing information for complete boxed warning.

Methylphenidate hydrochloride extended-release tablets have a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including methylphenidate hydrochloride extended-release tablets, can result in overdose and death (5.1, 9.2, 10):

- **Before prescribing methylphenidate hydrochloride extended-release tablets, assess each patient's risk for abuse, misuse, and addiction.**
- **Educate patients and their families about these risks, proper storage of methylphenidate hydrochloride extended-release tablets, and proper disposal of any unused drug.**
- **Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction.**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	09/2025
Dosage and Administration (2.3, 2.4)	02/2026
Warnings and Precautions: Long-Term Suppression of Growth in Pediatric Patients	09/2025
Warnings and Precautions: Removal Seizures and Hematologic Monitoring	02/2026

----------INDICATIONS AND USAGE----------

Methylphenidate hydrochloride extended-release tablets are a CNS stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients aged 6 to 65 years old (1).

Limitations of Use
The use of methylphenidate hydrochloride extended-release tablets are not recommended in pediatric patients younger than 6 years of age because they had higher plasma exposure and a higher incidence of adverse reactions (e.g., weight loss) than patients 6 years and older at the same dosage (5.7, 8.4).

----------DOSAGE AND ADMINISTRATION----------

- Prior to initiating methylphenidate hydrochloride extended-release tablets treatment assess for (2.1):
  - the presence of cardiac disease
  - for family history of tics or Tourette's syndrome and clinically evaluate patients for motor or verbal tics or Tourette's syndrome
- Administer once daily in the morning with or without food. Swallow whole with liquids; do not chew, divide, or crush (2.2).
- Recommended dosage in pediatric patients 6 to 17 years of age new to methylphenidate: starting dosage is 18 mg once daily. May be increased weekly in 18 mg increments.
  Maximum dosage for pediatric patients (2.3):
  - 6 to 12 years: 54 mg once daily
  - 13 to 17 years: 72 mg once daily
- Recommended dosage in adults (up to 65 years of age) new to methylphenidate: starting dosage is 18 mg or 36 mg once daily. May be increased weekly in 18 mg increments, up to 72 mg once daily (2.3).
- Patients currently using immediate-release methylphenidate: starting methylphenidate hydrochloride extended-release tablets dosage is based on current dosage regimen (2.4).

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

Extended-release tablets: 18, 27, 36, 54, and 72 mg (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to methylphenidate or other components of methylphenidate hydrochloride extended-release tablets (4)
- Receiving concomitant monoamine oxidase inhibitors and within 14 days following discontinuation of treatment with a MAO inhibitor (4)

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

- *Risks to Patients with Serious Cardiac Disease*: Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac disease (5.2).
- *Increased Blood Pressure and Heart Rate*: Monitor blood pressure and pulse (5.3).
- *Psychiatric Adverse Reactions*: Prior to initiating methylphenidate hydrochloride extended-release tablets, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing methylphenidate hydrochloride extended-release tablets (5.4).
- *Priapism*: If abnormally sustained or frequent and painful erections occur, patients should seek immediate medical attention (5.5).
- *Peripheral Vasculopathy, including Raynaud's Phenomenon*: Carefully assess for digital changes during methylphenidate hydrochloride extended-release tablets treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy (5.6).
- *Long-Term Suppression of Growth in Pediatric Patients*: Closely monitor growth (height and weight) in pediatric patients. Pediatric patients not growing or gaining height or weight as expected may need to have their methylphenidate hydrochloride extended-release tablets treatment interrupted (5.7).
- *Risk of Gastrointestinal (GI) Obstruction in Patients with GI Narrowing*: Only use in patients able to swallow the extended-release tablet whole, and should not ordinarily be used in patients with pre-existing severe GI narrowing (5.8).
- *Acute Angle Closure Glaucoma:* methylphenidate hydrochloride extended-release tablets-treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist (5.9).
- *Increased Intraocular Pressure (IOP) and Glaucoma*: Prescribe methylphenidate hydrochloride extended-release tablets to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Closely monitor patients with a history of increased IOP or open angle glaucoma (5.10).
- *Motor and Verbal Tics, and Worsening of Tourette's Syndrome*: Before initiating methylphenidate hydrochloride extended-release tablets, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome. Discontinue methylphenidate hydrochloride extended-release tablets treatment if clinically appropriate (5.11).

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

The most common adverse reactions (>5%) in double-blind clinical trials were:
Pediatric patients 6 to 17 years: upper abdominal pain (6.1).
Adults up to 65 years of age: decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, tachycardia, and hyperhidrosis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Trigen Laboratories, LLC at 1-800-444-5164 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).
See additional clinically significant drug interactions, in the DRUG INTERACTIONS section (7).

----------USE IN SPECIFIC POPULATIONS----------

Caution should be exercised if administered to nursing mothers (8.3)
Safety and efficacy has not been established in children less than six years old or elderly patients greater than 65 years of age (8.4 and 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA APPROVED MEDICATION GUIDE.

Revised: 04/2026

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE, MISUSE, AND ADDICTION

Methylphenidate hydrochloride extended-release tablets have a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including methylphenidate hydrochloride extended-release tablets, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with a higher dosage or unapproved methods of administration, such as snorting or injection.

Before prescribing methylphenidate hydrochloride extended-release tablets, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of methylphenidate hydrochloride extended-release tablets, and proper disposal of any unused drug. Throughout methylphenidate hydrochloride extended-release tablets treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction *[see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1, 9.2)]*.

1 INDICATIONS AND USAGE

Methylphenidate hydrochloride extended-release tablets are indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients aged 6 to 65 years old.

Limitations of Use

The use of methylphenidate hydrochloride extended-release tablets is not recommended in pediatric patients younger than 6 years of age because they had higher plasma exposure and a higher incidence of adverse reactions (e.g., weight loss) than patients 6 years and older at the same dosage *[see Warnings and Precautions (5.7), and Use in Specific Populations (8.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating patients with methylphenidate hydrochloride extended-release tablets, assess:

- For the presence of cardiac disease (e.g., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) *[see Warnings and Precautions (5.2)]*.
- The family history for tics or Tourette's syndrome and clinically evaluate patients for motor or verbal tics or Tourette's syndrome *[see Warnings and Precautions (5.11)]*.

2.2 Important Administration Instructions

Administer methylphenidate hydrochloride extended-release tablets orally once daily in the morning with or without food.

Swallow methylphenidate hydrochloride extended-release tablets whole with liquids. Do not split, crush, or chew the extended-release tablets because doing so will compromise the extended-release characteristics of methylphenidate hydrochloride extended-release tablets and may compromise the effectiveness or safety of methylphenidate hydrochloride extended-release tablets.

2.3 Recommended Methylphenidate Hydrochloride Extended-Release Tablets Dosage in Patients New to Methylphenidate

See Table 1 for the recommended once-daily dosage of methylphenidate hydrochloride extended-release tablets in

patients who were not taking a methylphenidate product. In patients who have not achieved an optimal response at a lower dosage, increase the methylphenidate hydrochloride extended-release tablets dosage in 18 mg increments at weekly intervals. However, if a slower titration is recommended for patients who have not achieved an optimal response taking 18 mg of methylphenidate hydrochloride extended-release tablets once daily, increase their daily dosage to 27 mg once per day.

Table 1: Recommended Methylphenidate Hydrochloride Extended-Release Tablets Dosage in Patients New to Methylphenidate

Patient Population	Recommended Starting Dosage	Dosage Range
Pediatric patients 6 to 12 years of age	18 mg once daily	18 mg to 54 mg once daily
Pediatric patients 13 to 17 years of age	18 mg once daily	18 mg to 72 mg once daily (not to exceed 2 mg/kg/day)
Adults 18 to 65 years of age	18 or 36 mg once daily	18 mg to 72 mg once daily

2.4 Recommended Methylphenidate Hydrochloride Extended-Release Tablets Dosage in Patients Switching from Another Methylphenidate Product

See Table 2 for the recommended starting dosage of methylphenidate hydrochloride extended-release tablets in patients switching from an immediate-release methylphenidate product administered twice daily or three times daily (total daily dosage of 10 to 60 mg/day).

Table 2: Recommended Starting Dosage in Patients Switching from Another Methylphenidate Product

Previous Immediate-release Methylphenidate Daily Dosage	Recommended Methylphenidate Hydrochloride Extended-Release Tablets Starting Dosage
5 mg twice daily or three times daily	18 mg every morning
10 mg twice daily or three times daily	36 mg every morning
15 mg twice daily or three times daily	54 mg every morning
20 mg twice daily or three times daily	72 mg every morning*

* Only for patients 13-65 years of age.

In patients who have not achieved an optimal response at a lower dosage, increase the methylphenidate hydrochloride extended-release tablets dosage in 18 mg increments at weekly intervals. The maximum recommended dosage in pediatric patients 6 to 12 years of age is 54 mg/day, and the maximum recommended dosage in patients 13-65 years old is 72 mg/day.

2.5 Dosage Reduction and Discontinuation

If paradoxical aggravation of ADHD symptoms or methylphenidate hydrochloride extended-release tablets-associated adverse reactions occur, reduce the methylphenidate hydrochloride extended-release tablets dosage or, if necessary, discontinue methylphenidate hydrochloride extended-release tablets.

If ADHD improvement is not observed after appropriate dosage modification over a one-month period, discontinue methylphenidate hydrochloride extended-release tablets.

3 DOSAGE FORMS AND STRENGTHS

Extended-Release Tablets:

- 18 mg tablets are yellow with “TL706” imprinted in black ink
- 27 mg tablets are gray with “TL707” imprinted in black ink

- 36 mg tablets are white with “TL708” imprinted in black ink
- 54 mg tablets are pink with “TL709” imprinted in black ink
- 72 mg tablets are blue with “TL710” imprinted in black ink

4 CONTRAINDICATIONS

Methylphenidate hydrochloride extended-release tablets are contraindicated in patients:

- Known to be hypersensitive to methylphenidate or other components of methylphenidate hydrochloride extended-release tablets. Hypersensitivity reactions, such as angioedema and anaphylactic reactions, have been reported in patients treated with methylphenidate hydrochloride extended-release tablets. *[see Adverse Reactions (6)]*.
- Receiving concomitant monoamine oxidase inhibitors (MAOIs), and within 14 days following discontinuation of treatment with a MAO inhibitor because of the risk of a hypertensive crisis *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Abuse, Misuse, and Addiction

Methylphenidate hydrochloride extended-release tablets have a high potential for abuse and misuse. The use of methylphenidate hydrochloride extended-release tablets exposes individuals to the risks of abuse and misuse, which can lead to the development of a substance use disorder, including addiction *[see Drug Abuse and Dependence (9.1, 9.2)]*. Misuse and abuse of CNS stimulants, including methylphenidate hydrochloride extended-release tablets, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher dosage or unapproved methods of administration, such as snorting or injection.

Before prescribing methylphenidate hydrochloride extended-release tablets, assess each patient’s risk for abuse, misuse, and addiction. Educate patients and their families about these risks and proper disposal of any unused drug. Advise patients to store methylphenidate hydrochloride extended-release tablets in a safe place, preferably locked, and instruct patients to not give methylphenidate hydrochloride extended-release tablets to anyone else. Throughout methylphenidate hydrochloride extended-release tablets treatment, reassess each patient’s risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

5.2 Risks to Patients with Serious Cardiac Disease

Sudden death has been reported in patients with structural cardiac abnormalities or other serious cardiac disease who were treated with CNS stimulants at the recommended ADHD dosage.

Avoid methylphenidate hydrochloride extended-release tablets use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease.

5.3 Increased Blood Pressure and Heart Rate

CNS stimulants may cause an increase in blood pressure (mean increase approximately 2 to 4 mm Hg) and heart rate (mean increase approximately 3 to 6 beats per minute) *[see Adverse Reactions (6)]*. Some patients may have larger increases.

Monitor all methylphenidate hydrochloride extended-release tablets-treated patients for hypertension and tachycardia.

5.4 Psychiatric Adverse Reactions

Exacerbation of Psychosis in Patients with a Psychotic Disorder

CNS stimulants, including methylphenidate hydrochloride extended-release tablets, may exacerbate behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants, including methylphenidate hydrochloride extended-release tablets, may induce a manic or mixed episode in patients with bipolar disorder. Prior to initiating methylphenidate hydrochloride extended-release tablets treatment, screen patients for risk factors for developing a manic episode (e.g., history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms in Patients without a History of a Bipolar or Psychotic Disorder

CNS stimulants (including methylphenidate hydrochloride extended-release tablets), at the recommended dosage, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. 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 with 0% of placebo-treated patients. If such symptoms occur, consider discontinuing methylphenidate hydrochloride extended-release tablets.

5.5 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate use in adult and pediatric male patients *[see Adverse Reactions (6)]*. Although priapism was not reported with methylphenidate initiation, priapism occurred in patients treated with methylphenidate after some time, often subsequent to an increase in dosage. Priapism also occurred during methylphenidate withdrawal (drug holidays or during discontinuation).

Methylphenidate hydrochloride extended-release tablets-treated 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 extended-release tablets, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon *[see Adverse Reactions (6.2)]*. Signs and symptoms of these cases of peripheral vasculopathy were usually intermittent and mild; however, sequelae have included digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports and at the therapeutic dosages of CNS stimulants in all age groups throughout the course of treatment. Signs and symptoms of peripheral vasculopathy generally improved after CNS stimulant dosage reduction or discontinuation.

During methylphenidate hydrochloride extended-release tablets treatment, carefully assess for digital changes. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for methylphenidate hydrochloride extended-release tablets-treated patients who develop signs or symptoms of peripheral vasculopathy.

5.7 Long-Term Suppression of Growth in Pediatric Patients

Methylphenidate hydrochloride extended-release tablets are not approved for use and are not recommended in pediatric patients below 6 years of age *[see Use in Specific Populations (8.4)]*. CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients.

Pediatric patients 7 to 13 years of age who received methylphenidate for 7 days per week for over 14 months to over 36 months had 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 development period.

Closely monitor growth (weight and height) in methylphenidate hydrochloride extended-release tablets-treated

pediatric patients. Pediatric patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

5.8 Risk of Gastrointestinal Obstruction in Patients with Gastrointestinal Narrowing

Because methylphenidate hydrochloride extended-release tablets are nondeformable and do not appreciably change in shape in the gastrointestinal (GI) tract, methylphenidate hydrochloride extended-release tablets should not ordinarily be administered to patients with pre-existing severe pathologic or iatrogenic GI narrowing. There have been rare reports of obstructive GI symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable modified-release dosage forms.

Methylphenidate hydrochloride extended-release tablets should be used only in patients who are able to swallow the extended-release tablets whole *[see Dosage and Administration (2.2)]*.

5.9 Acute Angle Closure Glaucoma

There have been reports of angle closure glaucoma associated with methylphenidate treatment.

Although the mechanism is not clear, methylphenidate hydrochloride extended-release tablets-treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist.

5.10 Increased Intraocular Pressure and Glaucoma

There have been reports of an elevation of intraocular pressure (IOP) associated with methylphenidate treatment *[see Adverse Reactions (6)]*.

Prescribe methylphenidate hydrochloride extended-release tablets to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Closely monitor methylphenidate hydrochloride extended-release tablets-treated patients with a history of abnormally increased IOP or open angle glaucoma.

5.11 Motor and Verbal Tics, and Worsening of Tourette's Syndrome

CNS stimulants, including methylphenidate, have been associated with the onset or exacerbation of motor and verbal tics *[see Adverse Reactions (6)]*. Worsening of Tourette's syndrome has also been reported.

Before initiating methylphenidate hydrochloride extended-release tablets, assess the family history for tics or Tourette's syndrome and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor methylphenidate hydrochloride extended-release tablets-treated patients for the emergence or worsening of tics or Tourette's syndrome, and discontinue methylphenidate hydrochloride extended-release tablets treatment if clinically appropriate.

6 ADVERSE REACTIONS

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

- Abuse, Misuse, and Addiction *[see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2)]*
- Hypersensitivity Reactions *[see Contraindications (4)]*
- Monoamine Oxidase Inhibitors *[see Contraindications (4), Drug Interactions (7)]*
- Risks to Patients with Serious Cardiac Disease *[see Warnings and Precautions (5.2)]*
- Increased Blood Pressure and Heart Rate *[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 in Pediatric Patients *[see Warnings and Precautions (5.7)]*
- Risks of Gastrointestinal Obstruction in Patients with Gastrointestinal Narrowing *[see Warnings and Precautions (5.8)]*
- Acute Angle Closure Glaucoma *[see Warnings and Precautions (5.9)]*
- Increased Intraocular Pressure and Glaucoma *[see Warnings and Precautions (5.10)]*
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trial Experience

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

The data below is based on a total of 3,906 patients in clinical studies who received methylphenidate hydrochloride extended-release tablets. Patients aged 6 up to 65 years old with ADHD were evaluated in 6 controlled clinical studies and 11 open-label clinical studies *[see Table 3]*.

Table 3: Methylphenidate Hydrochloride Extended-Release Tablets-treated Patients in Double-Blind and Open-Label Clinical Studies

Patient Population	**N**	**Dosage Range**
Pediatric patients 6 to 12 years of age	2,216	18 to 54 mg once daily
Adolescents	502	18 to 72 mg once daily
Adults up to 65 years of age	1,188	18 to 108 mg once daily

The most common adverse reactions (≥5%) in double-blind clinical trials were:

- Pediatric patients: upper abdominal pain *[see Table 4]*.
- Adults: decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, tachycardia, and hyperhidrosis *[see Table 5]*.

The most common adverse reactions associated with methylphenidate hydrochloride extended-release tablets discontinuation (≥1%) from the pediatric and adult clinical trials were anxiety, irritability, insomnia, and increased blood pressure.

Most Common Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials: Adverse reactions in either the pediatric or adult double-blind adverse reactions tables may be relevant for both patient populations.

Adverse Reactions in Pediatric Patients Aged 6 years and Older

Table 4 displays adverse reactions reported in 2% or more of methylphenidate hydrochloride extended-release tablets-treated pediatric patients ages 6 and older with ADHD in 4 placebo-controlled, double-blind clinical trials.

Table 4: Most Common Adverse Reactions[1] in Pediatric Patients 6 Years of Age and Older with ADHD in 4 Placebo-Controlled, Double-Blind Clinical Trials

	Methylphenidate Hydrochloride Extended-Release Tablets (n=321)	**Placebo (n=318)**
Upper abdominal pain	6%	4%
Insomnia[2]	3%	1%
Nasopharyngitis	3%	2%

Vomiting	3%	2%
Pyrexia	2%	1%

[1] Reported in ≥2% of methylphenidate hydrochloride extended-release tablets-treated patients
[2] Initial insomnia (methylphenidate hydrochloride extended-release tablets =0.6%) and insomnia (methylphenidate hydrochloride extended-release tablets =2.2%) terms were combined into Insomnia.

Adverse Reactions in Adults

Table 5 lists the adverse reactions reported in 2% or more of methylphenidate hydrochloride extended-release tablets-treated adults with ADHD in 2 placebo-controlled, double-blind clinical trials.

Table 5: Most Common Adverse Reactions[1] in Adults with ADHD in 2 Placebo-Controlled, Double-Blind Clinical Trials

	Methylphenidate Hydrochloride Extended-Release Tablets[2] (n=415)	**Placebo (n=212)**
Decreased appetite	25%	7%
Headache	22%	16%
Dry mouth	14%	4%
Nausea	13%	3%
Insomnia	12%	6%
Anxiety	8%	2%
Decreased weight	7%	3%
Dizziness	7%	5%
Irritability	6%	1%
Tachycardia	5%	0%
Hyperhidrosis	5%	1%
Depressed mood	4%	1%
Initial insomnia	4%	3%
Restlessness	3%	0%
Palpitations	3%	1%
Nervousness	3%	1%
Tremor	3%	1%
Upper respiratory tract infection	2%	1%
Agitation	2%	1%
Dyspepsia	2%	1%

[1] Reported in ≥2% of methylphenidate hydrochloride extended-release tablets-treated patients
[2] Included dosages up to 108 mg/day (1.5 times the maximum recommended dosage).

Other Adverse Reactions Observed in Clinical Trials of Methylphenidate Hydrochloride Extended-Release Tablets

The following adverse reactions occurred in less than 2% of methylphenidate hydrochloride extended-release tablets-treated patients ages 6 to 65 years of age in the double-blind and open-label clinical ADHD trials.

- *Blood and Lymphatic System Disorders:* Leukopenia
- *Cardiac Disorders:* Cardiac murmur, Hypertension, Heart rate increased
- *Ear and Labyrinth Disorders:* Vertigo
- *Eye Disorders:* Accommodation disorder, Dry eye, Vision blurred
- *Gastrointestinal Disorders:* Abdominal discomfort/pain, Constipation, Diarrhea, Vomiting
- *General Disorders and Administration Site Conditions:* Asthenia, Fatigue, Feeling jittery, Thirst

- *Hepatobiliary Disorders:* Hepatic enzymes increased
- *Infections and Infestations:* Sinusitis
- *Metabolism and Nutrition Disorders:* Anorexia
- *Musculoskeletal and Connective Tissue Disorders:* Muscle spasms, Muscle tightness
- *Nervous System Disorders:* Lethargy, Paresthesia, Psychomotor hyperactivity, Sedation, Somnolence, Tension headache
- *Psychiatric Disorders:* Affect lability, Aggression, Anger, Bruxism, Confusional state, Depression, Hypervigilance, decreased libido, Mood swings, Panic attack, Sleep disorder, Tearfulness, Tension, Tic
- *Reproductive System and Breast Disorders:* Erectile dysfunction
- *Respiratory, Thoracic and Mediastinal Disorders:* Cough, Dyspnea, Oropharyngeal pain
- *Skin and Subcutaneous Tissue Disorders:* Rash
- *Vascular Disorders:* Hot flush

Discontinuation Due to Adverse Reactions

In the 2 placebo-controlled studies in adults with ADHD, 25 (6%) methylphenidate hydrochloride extended-release tablets-treated patients and 6 (3%) placebo-treated patients discontinued due to an adverse reaction. In the methylphenidate hydrochloride extended-release tablets group, adverse reactions leading to discontinuation with an incidence of >0.5% were anxiety (1.7%), irritability (1.4%), increased blood pressure (1%), and nervousness (0.7%). In the placebo group, adverse reactions leading to discontinuation with an incidence of >0.5% were increased blood pressure (0.9%) and depressed mood (0.9%).

In the 11 open-label studies in patients 6 to 65 years of age with ADHD, 266 (7%) methylphenidate hydrochloride extended-release tablets-treated patients discontinued due to an adverse reaction including insomnia (1.2%), irritability (0.8%), anxiety (0.7%), decreased appetite (0.7%), and tic (0.6%).

Blood Pressure and Heart Rate Increases

- In the 1-week treatment, controlled trials in pediatric patients 6 to 12 years of age with ADHD (Studies 1 and 2) *[see Clinical Studies (14.2)]*, both the methylphenidate hydrochloride extended-release tablets once daily group and the methylphenidate three times daily group increased resting pulse by an average of 2 to 6 beats per minute (bpm) and increased the average systolic and diastolic blood pressure roughly 1 to 4 mm Hg during the day, relative to placebo.
- In the randomized withdrawal portion of the double-blind, placebo-controlled trial with pediatric patients 13 to 17 years of age with ADHD (Study 4) *[see Clinical Studies (14.3)]*, mean increases from baseline in resting pulse rate were observed with methylphenidate hydrochloride extended-release tablets and placebo at the end of the double-blind phase (5 and 3 beats/minute (bpm), respectively). At the end of four weeks of treatment, mean increases from baseline in blood pressure for methylphenidate hydrochloride extended-release tablets and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively.
- In the 7-week dose-titration, placebo-controlled study in adults 18 to 65 years of age with ADHD (Study 5) *[see Clinical Studies (14.4)]*, mean changes from baseline in resting pulse rate were 3.6 in methylphenidate hydrochloride extended-release tablets-treated patients and -1.6 for placebo-treated patients after 7 weeks of treatment. Mean changes from baseline in blood pressure after 7 weeks of treatment in methylphenidate hydrochloride extended-release tablets-treated and placebo-treated patients were –1.2 and –0.5 mm Hg (systolic) and 1.1 and 0.4 mm Hg (diastolic), respectively *[see Warnings and Precautions (5.3)]*.
- In the 5-week fixed-dose, placebo-controlled trial in adults 18 to 65 years of age with ADHD (Study 5) *[see*

Clinical Studies (14.4)], dose-dependent mean increases of 3.9 to 9.8 bpm from baseline in standing pulse rate were observed with methylphenidate hydrochloride extended-release tablets-treated patients and 2.7 bpm with placebo-treated patients at the end of 5 weeks. Mean changes from baseline in standing blood pressure after 5 weeks of treatment ranged from 0.1 to 2.2 mm Hg (systolic) and -0.7 to 2.2 mm Hg (diastolic) for methylphenidate hydrochloride extended-release tablets-treated patients and 1.1 mm Hg (systolic) and -1.8 mm Hg (diastolic) for placebo-treated patients.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of methylphenidate hydrochloride extended-release tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency:

- *Blood and Lymphatic System Disorders:* Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura
- *Cardiac Disorders:* Angina pectoris, Bradycardia, Supraventricular tachycardia, Ventricular extrasystoles
- *Eye Disorders:* Diplopia, Increased intraocular pressure, Mydriasis
- *General Disorders and Administration Site Conditions:* Chest pain, Drug effect decreased, Hyperpyrexia
- *Hepatobiliary Disorders:* Hepatocellular injury, Acute hepatic failure, Blood bilirubin increased
- *Immune System Disorders:* Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Exanthemas NEC
- *Investigations:* Blood alkaline phosphatase increased, Platelet count decreased
- *Musculoskeletal, Connective Tissue Disorders:* Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis
- *Nervous System Disorders:* Convulsion, Grand mal convulsion, Stroke in pediatric patients, Dyskinesia, Serotonin syndrome in combination with serotonergic drugs, Motor and Verbal Tics
- *Psychiatric Disorders:* Disorientation, Hallucination, Mania, Logorrhea
- *Reproductive System and Breast Disorders:* Priapism
- *Skin and Subcutaneous Tissue Disorders:* Alopecia, Bullous conditions, Erythema, Exfoliative conditions, Pruritus, Urticarias
- *Vascular Disorders:* Raynaud's phenomenon

7 DRUG INTERACTIONS

Table 6 describes clinically significant drug interactions with methylphenidate hydrochloride extended-release tablets.

Table 6: Clinically Significant Drug Interactions

Monoamine Oxidase Inhibitors	
Prevention or Management	Concomitant use of CNS stimulants, including methylphenidate hydrochloride extended-release tablets, with MAOIs or within 14 days after discontinuing an MAOI is contraindicated *[see Contraindications (4)]*.

Mechanism and Clinical Effect(s)	Concomitant use of MAOIs and CNS stimulants, including methylphenidate hydrochloride extended-release tablets, can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.
Antihypertensive Drugs	
Prevention or Management	Increase monitoring for blood pressure and adjust the dosage of the antihypertensive drug, as needed.
Mechanism and Clinical Effect(s)	Methylphenidate hydrochloride extended-release tablets may decrease effectiveness of drugs used to treat hypertension *[see Warnings and Precautions 5.3]*.
Halogenated Anesthetics	
Prevention or Management	Avoid use of methylphenidate hydrochloride extended-release tablets in patients being treated with anesthetics on the day of surgery.
Mechanism and Clinical Effect(s)	Concomitant use of halogenated anesthetics and methylphenidate hydrochloride extended-release tablets may increase the risk of sudden blood pressure and heart rate increase during surgery.
Risperidone	
Prevention or Management	Monitor for signs of extrapyramidal symptoms.
Mechanism and Clinical Effect(s)	The risk of risperidone-associated extrapyramidal symptoms may increase in patients taking concomitant methylphenidate hydrochloride extended-release tablets when there is a change in the methylphenidate hydrochloride extended-release tablets or risperidone dosage.

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 drugs, including methylphenidate hydrochloride extended-release tablets, during pregnancy. Healthcare providers are encouraged to advise patients to register by calling the National Pregnancy Registry for ADHD Medications at 1-866-961-2388 or visiting *https://womensmentalhealth.org/adhd-medications/*.

Risk Summary

Published studies and post-marketing reports on methylphenidate use during pregnancy have inconsistent findings about a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the fetus associated with the use of central nervous system (CNS) stimulants 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 throughout organogenesis at doses up to 4 and 16 times, respectively, the maximum recommended human dose (MRHD) of 72 mg/day given to adults on a mg/m^2 basis. However, spina bifida was observed in rabbits at a dose 54 times the MRHD given to adults. A slight decrease in body weight was observed in pregnant rats at the highest dose of 30 mg/kg/day (4 times the MRHD given to adults).

In a pre- and postnatal development study in which rats were treated with oral administration of methylphenidate throughout pregnancy and lactation, a decrease in pup body weight, alterations in sensory and neuromotor performance, and deficits in learning and memory were observed in both sexes at the highest dose (4 times the MRHD given to adults on a mg/m^2 basis) *(see Data)*.

The background risk of major birth defects and miscarriage in those with ADHD is unknown. All pregnancies have a background risk of birth defects, 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 extended-release tablets, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of a therapeutic dosage 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 up to 30 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 54 times the maximum recommended human dose (MRHD) of 72 mg/day given to adults on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (16 times the MRHD given to adults on a mg/m^2 basis).

There was no evidence of changes in morphological development in rats, although a reduction in maternal body weight was observed at the highest dose of 30 mg/kg/day (4 times the MRHD of 72 mg/day given to adults (on a mg/m^2 basis). The no effect level for maternal body weight in rats is 5 mg/day (equal to the MRHD for adults on a mg/m^2 basis); and the no effect level for embryo-fetal development is 30 mg/kg/day (4 times the MRHD for adults on a mg/m^2 basis).

When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 30 mg/kg/day, decreases in offspring body weight, alterations in sensory and neuromotor performance, and deficits in learning and memory were observed in both sexes at the highest dose (4 times the MRHD of 72 mg/day, given to adults on a mg/m^2 basis). The no effect level for pre- and post-natal development in rats was 12.5 mg/kg/day (2 times the MRHD given to adults on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Limited published literature, based on breast milk sampling from a small number of methylphenidate-treated lactating women, reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted methylphenidate dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant or effects on milk production. Long-term neurodevelopmental effects on infants from CNS stimulant exposure are unknown.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for methylphenidate hydrochloride extended-release tablets and any potential adverse effects on the breastfed child from methylphenidate hydrochloride extended-release tablets or from the underlying maternal

condition.

Clinical Considerations

Monitor breastfeeding infants of methylphenidate hydrochloride extended-release tablets-treated lactating women for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

8.4 Pediatric Use

The safety and effectiveness of methylphenidate hydrochloride extended-release tablets for the treatment of ADHD have been established in pediatric patients 6 years of age and older. The safety and effectiveness of methylphenidate hydrochloride extended-release tablets have not been established in pediatric patients below the age of 6 years.

In studies evaluating extended-release methylphenidate products, patients 4 to <6 years of age had higher systemic methylphenidate exposures than those observed in older pediatric patients at the same dosage. Pediatric patients 4 to <6 years of age also had a higher incidence of adverse reactions, including weight loss.

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Growth (weight and height) should be monitored in pediatric patients during treatment with CNS stimulants, including methylphenidate hydrochloride extended-release tablets. Pediatric patients who are not growing or gaining weight as expected may need to have their methylphenidate hydrochloride extended-release tablets 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 54 mg/day given to pediatric patients 6 to 12 years of age on a mg/m^2 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 54 mg/day given to pediatric patients 6 to 12 years of age 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 (9 times the MRHD given to pediatric patients 6 to 12 years of age on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (approximately 0.4 times the MRHD given to pediatric patients 6 to 12 years of age on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use

Methylphenidate hydrochloride extended-release tablets are not indicated for use in patients greater than 65 years of age.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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

9.2 Abuse

Methylphenidate hydrochloride extended-release tablets have a high potential for abuse and misuse which can

lead to the development of a substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*.

Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of methylphenidate hydrochloride extended-release tablets may cause increased heart rate, respiratory rate, or blood pressure; 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 with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including methylphenidate hydrochloride extended-release tablets, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Studies of Abuse Potential with Methylphenidate Hydrochloride Extended-Release Tablets

In two placebo- and active-controlled, crossover human abuse potential (HAP) studies, the relative abuse potential of single oral doses of methylphenidate hydrochloride extended-release tablets were compared to single oral doses of immediate-release methylphenidate (IR MPH) and placebo in subjects with a history of recreational CNS stimulant use. In these studies, the response for each of the abuse-related subjective measures was defined as the maximum effect within the first 8 hours after treatment administration. When evaluating these results, consider that 22% of the total methylphenidate amount in methylphenidate hydrochloride extended-release tablets are available for immediate release and the remaining 78% is available for extended-release over 24 hours.

- In the first HAP study (n=40), single dose administration of methylphenidate hydrochloride extended-release tablets 108 mg (1.5 times the maximum recommended adult dose of methylphenidate hydrochloride extended-release tablets), IR MPH 60 mg (2 times the maximum recommended adult dose of IR MPH), or placebo were administered to subjects in a cross-over design. Methylphenidate hydrochloride extended-release tablets 108 mg and IR MPH 60 mg produced responses on the subjective measures of Drug Liking and Abuse Potential that were statistically similar, and both were statistically significantly greater than the responses to placebo. However, on subjective measures of Euphoria, methylphenidate hydrochloride extended-release tablets 108 mg produced responses that were statistically less than those produced by IR MPH 60 mg.
- In the second HAP study (n=49), a single dose of methylphenidate hydrochloride extended-release tablets 108 mg (1.5 times the maximum recommended adult dose of methylphenidate hydrochloride extended-release tablets), methylphenidate hydrochloride extended-release tablets 54 mg (0.75 times the maximum recommended adult dose of methylphenidate hydrochloride extended-release tablets), IR MPH 90 mg (3 times the maximum recommended adult dose of IR MPH), 50 mg (1.7 times the maximum recommended adult dose of IR MPH), or placebo were administered to subjects in a cross-over design. The three active treatments each produced responses on the subjective measure of Drug Liking that were statistically significantly greater than responses to placebo. IR MPH produced greater responses on Drug Liking compared to methylphenidate hydrochloride extended-release tablets when similar doses were compared (50 mg vs. 54 mg, and 90 mg vs. 108 mg, respectively), consistent with the extended-release properties of methylphenidate hydrochloride extended-release tablets. However, there were no significant differences in response between methylphenidate hydrochloride extended-release tablets 108 mg and IR MPH 50 mg on the subjective measures of Drug Liking and Euphoria.

The clinical significance of the differences in response between methylphenidate hydrochloride extended-release tablets and IR MPH on subjective measures of abuse potential as reported in these HAP studies is unknown.

9.3 Dependence

Physical Dependence

Methylphenidate hydrochloride extended-release tablets may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal signs and symptoms after abrupt discontinuation or dosage reduction following prolonged use of CNS stimulants including methylphenidate hydrochloride extended-release tablets included dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

Tolerance

Methylphenidate hydrochloride extended-release tablets may produce tolerance. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

10 OVERDOSAGE

10.1 Clinical Effects of Overdose

Overdose of CNS stimulants is characterized by the following sympathomimetic effects:

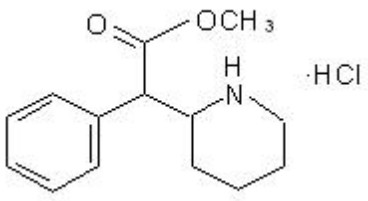
- Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden cardiac death. Takotsubo cardiomyopathy may develop.
- CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin syndrome, seizures, cerebral vascular accidents, and coma may occur.
- Life-threatening hyperthermia (temperatures greater than 104°F) and rhabdomyolysis may develop.

10.2 Overdose Management

Consider the possibility of multiple drug ingestion. The pharmacokinetic profile of methylphenidate hydrochloride extended-release tablets should be considered when treating patients with overdose. Because methylphenidate has a large volume of distribution and is rapidly metabolized, dialysis is not useful. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

Methylphenidate hydrochloride extended-release tablets, USP are a central nervous system (CNS) stimulant. Methylphenidate hydrochloride extended-release tablets, USP are available in five tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, 54, or 72 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. Chemically, methylphenidate HCl is d,l (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is $C_{14}H_{19}NO_2$•HCl. Its structural formula is:



Methylphenidate HCl USP is a white, odorless 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.

Methylphenidate hydrochloride extended-release tablets, USP also contain the following inactive ingredients: black iron oxide, cellulose acetate, colloidal silicon dioxide, ferrosoferric oxide, hypromellose, lactose monohydrate, magnesium stearate, phosphoric acid, polyethylene glycol, polyethylene oxide, sodium chloride, succinic acid, titanium dioxide, triacetin. In addition,

18 mg tablets contain: iron oxide red, iron oxide yellow

27 mg tablets contain: FD&C Yellow #6 Aluminum Lake, FD&C Blue #2 Aluminum Lake, FD&C Red #40 Aluminum Lake

54 mg tablets contain: FD&C Yellow #6 Aluminum Lake, FD&C Red #40 Aluminum Lake, FD&C Blue #2 Aluminum Lake

72 mg tablets contain: FD&C Blue #1 Aluminum Lake

FDA approved dissolution test specifications differ from USP

11.1 System Components and Performance

Methylphenidate hydrochloride extended-release tablets use osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active bilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within one hour, providing an initial dose of methylphenidate. Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The membrane controls the rate at which water enters the tablet core, which in turn controls drug delivery. Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug-concentration gradient incorporated into the drug layer of core of methylphenidate hydrochloride extended-release tablets. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell along with insoluble core components. It is possible that methylphenidate hydrochloride extended-release tablets may be visible on abdominal x-rays under certain circumstances, especially when digital enhancing techniques are utilized.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate is a central nervous system (CNS) stimulant. The mode of therapeutic action of methylphenidate in the treatment of ADHD is not known. Methylphenidate blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increases the release of these monoamines into the extraneuronal space.

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer. The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of methylphenidate hydrochloride extended-release tablets has not been fully characterized.

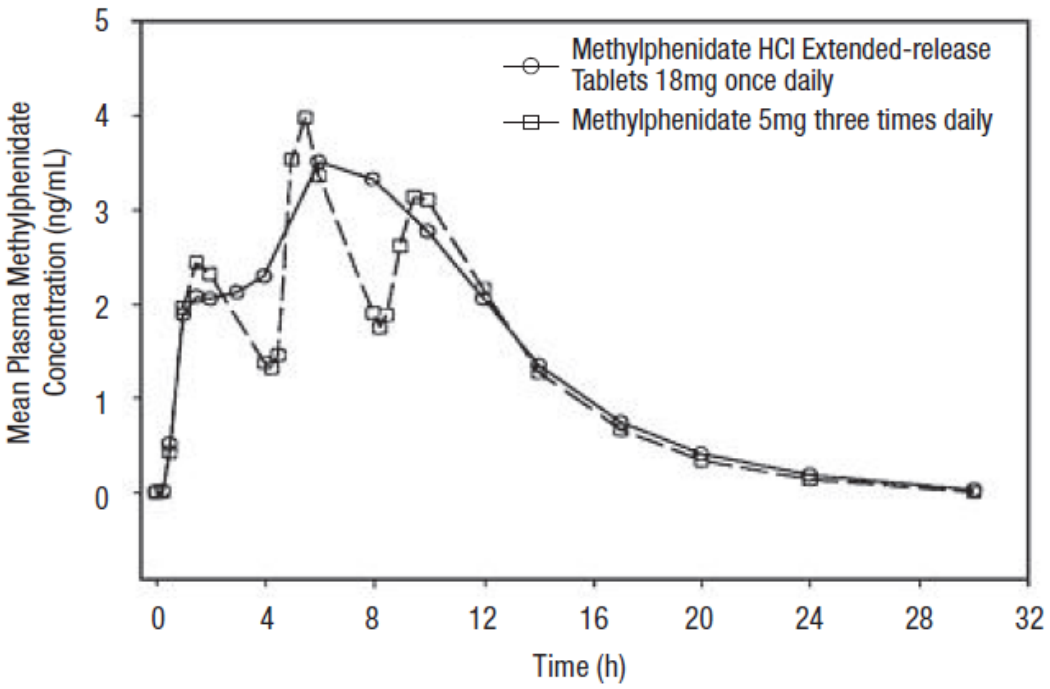
12.3 Pharmacokinetics

Absorption

Following oral administration of methylphenidate hydrochloride extended-release tablets, plasma methylphenidate concentrations reached an initial maximum concentration at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours, after which a gradual decrease begins. Mean times to reach peak plasma concentrations across all doses of methylphenidate hydrochloride extended-release tablets occurred between 6 and 10 hours.

Methylphenidate hydrochloride extended-release tablets once daily minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily [*see Figure 1*]. No clinically significant difference in methylphenidate exposures was observed following the administration of either methylphenidate hydrochloride extended-release tablets once daily and immediate-release methylphenidate three times daily in adults.

Figure 1. Mean Methylphenidate Plasma Concentrations Following a Single 18 mg Methylphenidate Hydrochloride Extended-Release Tablets dose and Immediate-release Methylphenidate 5 mg Doses (Three Doses Administered Every 4 Hours)



The mean single-dose pharmacokinetic parameters in 36 healthy adults following the administration of one 18 mg methylphenidate hydrochloride extended-release tablets dose and three 5 mg methylphenidate doses every four hours are summarized in Table 7.

Table 7: Methylphenidate Pharmacokinetic Parameters (Mean ± SD) After Methylphenidate Hydrochloride Extended-Release Tablets and Immediate-release Methylphenidate Dosing in Healthy Adults

Parameters	Methylphenidate Hydrochloride Extended-Release Tablets (18 mg single dose) (n=36)	Immediate-release Methylphenidate (Three 5 mg doses every four hours) (n=35)
C_{max} (ng/mL)	3.7 ± 1.0	4.2 ± 1.0
T_{max} (h)	6.8 ± 1.8	6.5 ± 1.8
AUC_{inf} (ng·h/mL)	41.8 ± 13.9	38.0 ± 11.0
$t_{½}$ (h)	3.5 ± 0.4	3.0 ± 0.5

The methylphenidate pharmacokinetics were evaluated in healthy adults following single- and multiple-doses (steady state) of methylphenidate hydrochloride extended-release tablets (up to 144 mg/day (up to 2 times the maximum recommended dose)). The mean half-life was about 3.6 hours. No differences in the pharmacokinetics of methylphenidate hydrochloride extended-release tablets were noted following single and repeated once-daily methylphenidate hydrochloride extended-release tablets dosing, indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated once-daily dosing are similar to those following a single 18 to 144 mg dose of methylphenidate hydrochloride extended-release tablets.

Dose Proportionality

Following administration of methylphenidate hydrochloride extended-release tablets in single doses of 18, 36, and 54 mg/day to healthy adults, C_{max} and $AUC_{(0–inf)}$ of d-methylphenidate were dose proportional, whereas l-methylphenidate C_{max} and $AUC_{(0–inf)}$ increased disproportionately with respect to dose. Following administration of methylphenidate hydrochloride extended-release tablets, plasma concentrations of the l-isomer were approximately 1/40 the plasma concentrations of the d-isomer.

In healthy adults, single and multiple doses (once-daily) methylphenidate hydrochloride extended-release tablets doses from 54 to 144 mg/day resulted in linear and dose-proportional increases in C_{max} and AUC_{inf} for total methylphenidate (MPH) and its major metabolite, α-phenyl-piperidine acetic acid (PPAA). There was no time dependency in the pharmacokinetics of methylphenidate. The ratio of metabolite (PPAA) to parent drug (MPH) was constant across doses from 54 to 144 mg/day, both after single dose and upon multiple dosing.

In a multiple-dose study, after patients aged 13 to 16 with ADHD were administered their prescribed methylphenidate hydrochloride extended-release tablets dose (18 to 72 mg/day), mean C_{max} and AUC_{TAU} of d- and total methylphenidate increased proportionally with respect to dose.

Food Effects: In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of methylphenidate hydrochloride extended-release tablets when administered after a high-fat breakfast.

Distribution

Plasma methylphenidate concentrations in adults and adolescents decline biexponentially following oral methylphenidate hydrochloride extended-release tablets administration. The half-life of methylphenidate in adults and adolescents following oral methylphenidate hydrochloride extended-release tablets administration was approximately 3.5 hours.

Elimination

Metabolism: In humans, methylphenidate is metabolized primarily by de-esterification to PPAA, which has little or no pharmacologic activity. In adults the metabolism of methylphenidate hydrochloride extended-release tablets once daily as evaluated by metabolism to PPAA is similar to that of immediate-release methylphenidate three times daily. The metabolism of single and repeated once-daily doses of methylphenidate hydrochloride extended-

release tablets is similar.

Excretion: After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose.

Alcohol Effect on Methylphenidate Release in Methylphenidate Hydrochloride Extended-Release Tablets

*In-vitr*o studies were conducted to explore the effect of alcohol on the release characteristics of methylphenidate for all five strengths of methylphenidate hydrochloride extended-release tablets. At alcohol concentrations up to 40%, there was no increased release of methylphenidate in the first two hours.

Specific Populations

Male and Female Patients:

In healthy adults, the mean dose-adjusted $AUC_{(0–inf)}$ values for methylphenidate hydrochloride extended-release tablets were 36.7 ng·h/mL in males and 37.1 ng·h/mL in females, with no differences noted between the two groups.

Ethnic Groups:

In adults receiving methylphenidate hydrochloride extended-release tablets, dose-adjusted $AUC_{(0–inf)}$ was consistent across ethnic groups; however, the sample size was insufficient to detect ethnic variations in pharmacokinetics.

Pediatric Patients:

Increase in pediatric age was associated with increased apparent oral clearance (CL/F) (58% increase in adolescents compared to younger pediatric patients). Some of these differences could be explained by body-weight differences among these populations. This suggests that subjects with higher body weight may have a lower exposure of total methylphenidate at similar doses.

Patients with Renal Impairment

There is no pharmacokinetic information on the use of methylphenidate hydrochloride extended-release tablets in patients with renal impairment.

Patients with Hepatic Impairment

There is no pharmacokinetic information on the use of methylphenidate hydrochloride extended-release tablets in patients with hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

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 4 times the maximum recommended human dose (MRHD) of methylphenidate hydrochloride extended-release tablets given to adults on a mg/m^2 basis. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

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 6 times the MRHD (adults) on a mg/m^2 basis.

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.

Mutagenesis

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or 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 cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus assay.

Impairment of Fertility

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 11 times the MRHD of methylphenidate hydrochloride extended-release tablets given to adults on a mg/m^2 basis.

14 CLINICAL STUDIES

14.1 Overview of Clinical Trials

Methylphenidate hydrochloride extended-release tablets were demonstrated to be effective in the treatment of ADHD in patients who met the Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD in the following trials:

- Three trials in pediatric patients 6 to 12 years old (Studies 1, 2, and 3),
- One trial in adolescents (13 to 18 years old),
- Two trials in adults (18 to 65 years old).

14.2 Clinical Trials in Pediatric Patients 6 to 12 Years

Three double-blind, active- and placebo-controlled trials were conducted in 416 pediatric patients 6 to 12 years of age with ADHD: (1) two single-center, crossover trials (patients received each treatment for one week) (Studies 1 and 2) and (2) a multicenter, 4-week, parallel-group comparison trial (Study 3). In these trials, patients were randomized to receive:

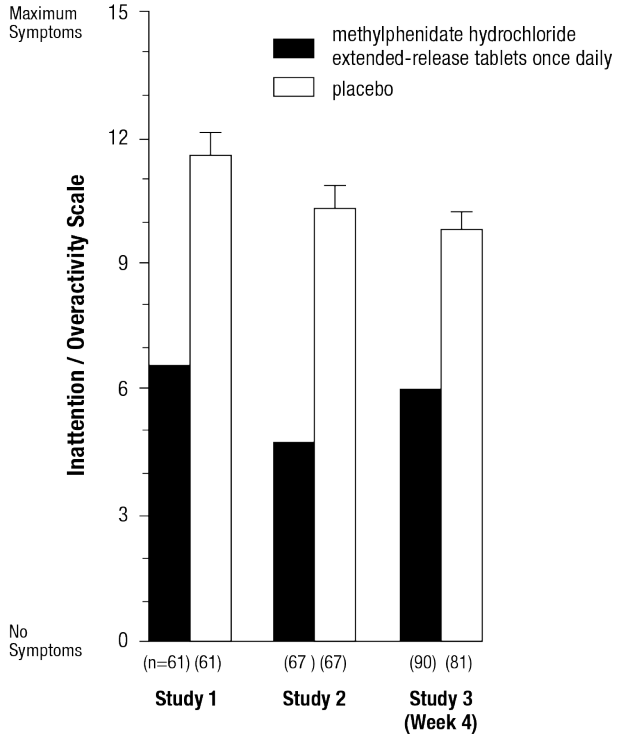
- 18 mg, 36 mg, or 54 mg of oral methylphenidate hydrochloride extended-release tablets given once daily,
- 5 mg, 10 mg, or 15 mg of oral immediate-release methylphenidate given three times daily (15, 30, or 45 mg total daily dosage) over 12 hours, and
- Placebo

The primary comparison of interest in all three trials was the methylphenidate hydrochloride extended-release tablets group versus the placebo group.

ADHD symptoms were evaluated by community schoolteachers using the Inattention/Overactivity with Aggression (IOWA) Conners scale.

A statistically significant reduction in the Inattention/Overactivity subscale (0 to 15) in the methylphenidate hydrochloride extended-release tablets group versus the placebo group was shown in all three trials. The scores for methylphenidate hydrochloride extended-release tablets and placebo for the three trials are presented in Figure 2.

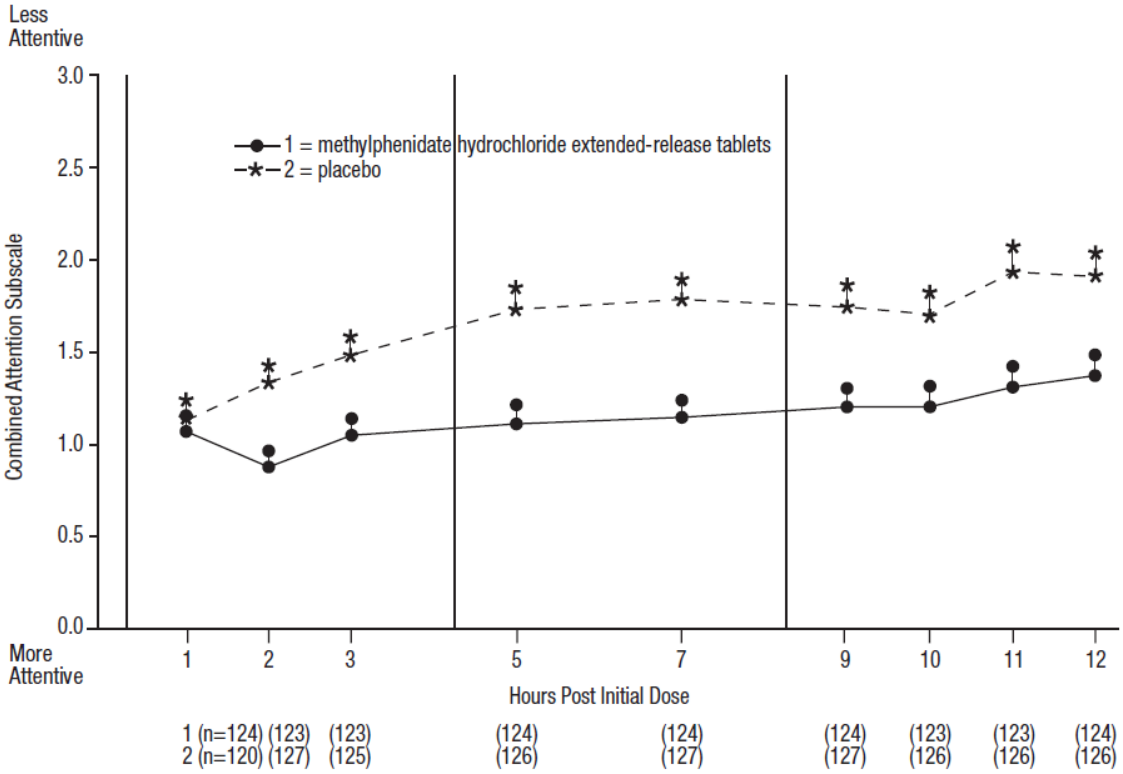
Figure 2. Mean Community School Teacher Inattention/Overactivity Subscores in the IOWA Conners Scale in Pediatric Patients 6 to 12 Years with ADHD



Studies 1 and 2 involved a 3-way crossover of 1-week per treatment arm. Study 3 involved 4 weeks of parallel-group treatments with a Last Observation Carried Forward analysis at week 4. Error bars represent the mean plus standard error of the mean.

In Studies 1 and 2, symptoms of ADHD including attentiveness were evaluated by schoolteachers using the Swanson, Kotkin, Agler, M-Fynn, and Pelham (SKAMP) laboratory school rating scale. The combined results from these two trials demonstrated statistically significant improvements in attention and behavior in the methylphenidate hydrochloride extended-release tablets group compared to the placebo group. These results were maintained through 12 hours after dosing. Figure 3 presents the schoolteacher SKAMP ratings for the methylphenidate hydrochloride extended-release tablets and placebo groups in Studies 1 and 2.

Figure 3. School Teacher SKAMP Ratings (Mean (SEM) of Combined Attention) in Pediatric Patients 6 to 12 Years with ADHD (Studies 1 and 2)



Note: Mean and mean plus standard error of mean shown

14.3 Clinical Trials in Pediatric Patients 13 to 17 Years

In a randomized-withdrawal, double-blind, multicenter, placebo-controlled trial (Study 4) with 177 pediatric patients 13 to 17 years of age with ADHD, methylphenidate hydrochloride extended-release tablets demonstrated effectiveness with a dosage up to 72 mg/day (1.4 mg/kg/day):

- Of 220 patients who entered an open 4-week titration phase, 177 patients were titrated to an individualized methylphenidate hydrochloride extended-release tablets dosage (maximum of 72 mg/day) based on meeting specific improvement criteria on the ADHD Rating Scale and the Global Assessment of Effectiveness with acceptable tolerability.
- Patients who met these criteria were then randomized to receive either their individualized dosage of methylphenidate hydrochloride extended-release tablets (18 – 72 mg/day, n=87) or placebo (n=90) during a two-week double-blind phase.

At the end of the double blind phase, mean scores for the investigator rating on the ADHD Rating Scale demonstrated that the methylphenidate hydrochloride extended-release tablets group were statistically significantly superior to the placebo group.

14.4 Clinical Trials in Adults up to 65 Years Old

Two randomized double-blind, placebo-controlled multicenter, parallel-group trials were conducted in 627 adults aged 18 to 65 years with ADHD who received methylphenidate hydrochloride extended-release tablets or placebo once daily:

- Study 5 was a 7-week, dose-titration trial where patients were randomized to receive methylphenidate hydrochloride extended-release tablets (n=110) or placebo (n=116) once daily. Patients treated with methylphenidate hydrochloride extended-release tablets started at 36 mg/day and had incremental increases of 18 mg/day up to 108 mg/day of methylphenidate hydrochloride extended-release tablets (titration was based on improvement criteria with acceptable tolerability).
- Study 6 was a 5-week, fixed-dose trial where patients were randomized to receive 18 mg (n=101), 36 mg (n=102), or 72 mg (n=102) of methylphenidate hydrochloride extended-release tablets versus placebo (n=96) once daily.

In Study 5, methylphenidate hydrochloride extended-release tablets demonstrated efficacy based on the change from baseline to final study visit on the Adult ADHD Investigator Rating Scale (AISRS). At the final study visit, mean change scores (LS Mean, SEM) for the investigator rating on the AISRS demonstrated that the methylphenidate hydrochloride extended-release tablets group were statistically significantly superior to the placebo group.

In Study 6, all three methylphenidate hydrochloride extended-release tablets dosages were statistically significantly more effective than placebo in improving Conners' Adult ADHD Rating Scale (CAARS) total scores after five weeks of treatment.

16 HOW SUPPLIED/STORAGE AND HANDLING

Methylphenidate hydrochloride extended-release tablets, USP are available in 18, 27, 36, 54, and 72 mg strengths.

- 18 mg tablets are yellow with “TL706” imprinted in black ink
- 27 mg tablets are gray with “TL707” imprinted in black ink
- 36 mg tablets are white with “TL708” imprinted in black ink
- 54 mg tablets are pink with “TL709" imprinted in black ink
- 72 mg tablets are blue with “TL710” imprinted in black ink.

The tablets are supplied:

18 mg	100-count bottle	NDC 13811-706-10
27 mg	100-count bottle	NDC 13811-707-10
36 mg	100-count bottle	NDC 13811-708-10
54 mg	100-count bottle	NDC 13811-709-10
72 mg	30-count bottle	NDC 13811-710-30

Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

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

Abuse, Misuse, and Addiction

Educate patients and their families about the risks of abuse, misuse, and addiction of methylphenidate hydrochloride extended-release tablets, which can lead to overdose and death, and proper disposal of any unused drug *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.1, 9.2), Overdosage (10)]*. Advise patients to store methylphenidate hydrochloride extended-release tablets in a safe place, preferably locked, and instruct patients to not give methylphenidate hydrochloride extended-release tablets to anyone else.

Risks to Patients with Serious Cardiac Disease

Advise patients that there are potential risks to patients with serious cardiac disease, including sudden death, with methylphenidate hydrochloride extended-release tablets use. Instruct patients to contact a healthcare provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease *[see Warnings and Precautions (5.2)]*.

Increased Blood Pressure and Heart Rate

Advise patients and their caregivers that methylphenidate hydrochloride extended-release tablets can cause elevations in blood pressure and heart rate *[see Warnings and Precautions (5.3)]*.

Psychiatric Risks

Advise patients and their caregivers that methylphenidate hydrochloride extended-release tablets, at recommended doses, can cause psychotic or manic symptoms, even in patients without a prior history of psychotic symptoms or mania *[see Warnings and Precautions (5.4)]*.

Priapism

Advise patients, caregivers, and family members of methylphenidate hydrochloride extended-release tablets-treated males of the possibility of priapism. Instruct the patient to seek immediate medical attention in the event of priapism *[see Warnings and Precautions (5.5)]*.

Peripheral Vasculopathy, including Raynaud's Phenomenon

Instruct patients about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms; to report to their healthcare provider any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes; to call their healthcare provider immediately with any signs of unexplained wounds appearing on fingers or toes while taking methylphenidate hydrochloride extended-release tablets *[see Warnings and Precautions (5.6)]*.

Long-term Suppression of Growth in Pediatric Patients

Advise patients, caregivers, and family members that methylphenidate hydrochloride extended-release tablets may cause slowing of growth and weight loss in pediatric patients *[see Warnings and Precautions (5.7)]*.

Glaucoma and Increased Intraocular Pressure

Advise patients that increased intraocular pressure and glaucoma may occur during methylphenidate hydrochloride extended-release tablets treatment *[see Warnings and Precautions (5.10)]*.

Motor and Verbal Tics, and Worsening of Tourette's Syndrome

Advise patients that motor and verbal tics and worsening of Tourette's Syndrome may occur during methylphenidate hydrochloride extended-release tablets treatment. Instruct patients to notify their healthcare provider if emergence of new tics or worsening of tics or Tourette's syndrome occurs *[see Warnings and Precautions (5.11)]*.

Administration Instructions

Instruct patients to swallow methylphenidate hydrochloride extended-release tablets whole with liquids, and not to split, crush, or chew, the extended-release tablets. Advise patients not to be concerned if they occasionally notice a tablet-appearing substance in their stool.

Pregnancy

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to methylphenidate hydrochloride extended-release tablets during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise methylphenidate hydrochloride extended-release tablets-treated breastfeeding women to monitor their infants for agitation, poor sleeping patterns, changes in feeding, and reduced weight gain *[see Use in Specific Populations (8.2)]*.

For more information call 1-800-444-5164.

Manufactured for:
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MEDICATION GUIDE
Methylphenidate hydrochloride extended-release tablets USP CII
(METH-il-FEN-i-date)

What is the most important information I should know about methylphenidate hydrochloride extended-release tablets?

Methylphenidate hydrochloride extended-release tablets may cause serious side effects, including:

- **Abuse, misuse, and addiction.** Methylphenidate hydrochloride extended-release tablets have a high chance for abuse and misuse and may lead to substance use problems, including addiction. Misuse and abuse of methylphenidate hydrochloride extended-release tablets, other methylphenidate containing medicines, and amphetamine containing medicines, can lead to overdose and death. The risk of overdose and death is increased with higher doses of methylphenidate hydrochloride extended-release tablets or when it is used in ways that are not approved, such as snorting or injection.
    - Your healthcare provider should check you or your child's risk for abuse, misuse, and addiction before starting treatment with methylphenidate hydrochloride extended-release tablets and will monitor you or your child during treatment.
    - Methylphenidate hydrochloride extended-release tablets may lead to physical dependence after prolonged use, even if taken as directed by your healthcare provider.
    - Do not give methylphenidate hydrochloride extended-release tablets to anyone else. See "**What are methylphenidate hydrochloride extended-release tablets?**" for more information.

- Keep methylphenidate hydrochloride extended-release tablets in a safe place and properly dispose of any unused medicine. See "**How should I store methylphenidate hydrochloride extended-release tablets?**" for more information.
- Tell your healthcare provider if you or your child have ever abused or been dependent on alcohol, prescription medicines, or street drugs.

- **Risks for people with serious heart disease.** Sudden death has happened in people who have heart defects or other serious heart disease.

Your healthcare provider should check you or your child carefully for heart problems before starting treatment with methylphenidate hydrochloride extended-release tablets. Tell your healthcare provider if you or your child have any heart problems, heart disease, or heart defects.

Call your healthcare provider or go to the nearest hospital emergency room right away if you or your child have any signs of heart problems, such as chest pain, shortness of breath, or fainting during treatment with methylphenidate hydrochloride extended-release tablets.

- **Increased blood pressure and heart rate.**
  Your healthcare provider should check your or your child's blood pressure and heart rate regularly during treatment with methylphenidate hydrochloride extended-release tablets.

- **Mental (psychiatric) problems, including:**
  - new or worse behavior or thought problems
  - new or worse bipolar illness
  - new psychotic symptoms (such as hearing voices, or seeing or believing things that are not real) or new manic symptoms

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

Call your healthcare provider right away if you or your child have any new or worsening mental symptoms or problems during treatment with methylphenidate hydrochloride extended-release tablets, especially hearing voices, seeing or believing things that are not real, or new manic symptoms.

See **"What are the possible side effects of methylphenidate hydrochloride extended-release tablets?"** for more information about side effects.

What are methylphenidate hydrochloride extended-release tablets?

Methylphenidate hydrochloride extended-release tablets are a central nervous system (CNS) stimulant prescription medicine used for the treatment of attention deficit hyperactivity disorder (ADHD) in people 6 to 65 years of age. Methylphenidate hydrochloride extended-release tablets may help increase attention and decrease impulsiveness and hyperactivity in people with ADHD.

Methylphenidate hydrochloride extended-release tablets are not recommended for use in children under 6 years of age with ADHD.

Methylphenidate hydrochloride extended-release tablets are a federally controlled substance (CII) because it contains methylphenidate that can be a target for people who abuse prescription medicines or street drugs. Keep methylphenidate hydrochloride extended-release tablets in a safe place to protect it from theft. Never give your methylphenidate hydrochloride extended-release tablets to anyone else because it may cause death or harm them. Selling or giving away methylphenidate hydrochloride extended-release tablets may harm others and is against the law.

Who should not take methylphenidate hydrochloride extended-release tablets?

Do not take methylphenidate hydrochloride extended-release tablets if you or your child are:

- allergic to methylphenidate or any of the ingredients in methylphenidate hydrochloride extended-release tablets. See the end of this Medication Guide for a complete list of ingredients in methylphenidate hydrochloride extended-release tablets.
- taking, or have stopped taking within the past 14 days, a medicine called a monoamine oxidase inhibitor (MAOI)

Before taking methylphenidate hydrochloride extended-release tablets, tell your healthcare provider about all of your or your child's medical conditions, including if you or your child:

- have heart problems, heart disease, heart defects, or high blood pressure
- have mental problems including psychosis, mania, bipolar illness, or depression, or have a family history of suicide, bipolar illness, or depression
- have circulation problems in fingers and toes
- have had a blockage or narrowing of the intestines
- have eye problems, including increased pressure in your eye, glaucoma, or problems with your close-up vision (farsightedness)
- have or had repeated movements or sounds (tics) or Tourette's syndrome, or have a family history of tics or Tourette's syndrome
- are pregnant or plan to become pregnant. It is not known if methylphenidate hydrochloride extended-release tablets will harm the unborn baby.
    - There is a pregnancy exposure registry for women are exposed to methylphenidate hydrochloride extended-release tablets during pregnancy. The purpose of the registry is to collect information about the health of women exposed to methylphenidate hydrochloride extended-release tablets and their baby. If you or your child becomes pregnant during treatment with methylphenidate hydrochloride extended-release tablets, talk to your healthcare provider about registering with the National Pregnancy Registry for ADHD Medications at 1-866-961-2388 or visit online at https://womensmentalhealth.org/adhd-medications/.
- are breastfeeding or plan to breastfeed. Methylphenidate hydrochloride extended-release tablets passes into the breast milk. Talk to your healthcare provider about the best way to feed the baby during treatment with methylphenidate hydrochloride extended-release tablets. If you breastfeed during treatment with methylphenidate hydrochloride extended-release tablets, monitor your baby for agitation, poor sleeping patterns, changes in feeding, and reduced weight gain.

Tell your healthcare provider about all of the medicines that you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Methylphenidate hydrochloride extended-release tablets and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be changed during treatment with methylphenidate hydrochloride extended-release tablets. Your healthcare provider will decide whether methylphenidate hydrochloride extended-release tablets can be taken with other medicines.

Especially tell your healthcare provider if you or your child take:

- a medicine to treat blood pressure (anti-hypertensive)
- risperidone

Know the medicines that you or your child take. Keep a list of your or your child's medicines with you to show your healthcare provider and pharmacist when you or your child get a new medicine.

Do not start any new medicine during treatment with methylphenidate hydrochloride extended-release tablets without first talking to your healthcare provider.

How should I take methylphenidate hydrochloride extended-release tablets?

- Take methylphenidate hydrochloride extended-release tablets exactly as prescribed by your or your child's healthcare provider.
- Your healthcare provider may change the dose or tell you to stop taking methylphenidate hydrochloride extended-release tablets if needed.
- Take methylphenidate hydrochloride extended-release tablets 1 time each day in the morning with or without food.
- Swallow methylphenidate hydrochloride extended-release tablets whole with water or other liquids. **Do not split, crush, or chew the tablets.** Tell your healthcare provider if you or your child cannot swallow methylphenidate hydrochloride extended-release tablets whole. A different medicine will need to be prescribed.
- Methylphenidate hydrochloride extended-release tablets do not dissolve completely in the body after all the medicine has been released. You or your child may sometimes notice the empty tablet in a bowel movement. This is normal.
- If you or your child take too much methylphenidate hydrochloride extended-release tablets, call your healthcare provider or Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of methylphenidate hydrochloride extended-release tablets?

Methylphenidate hydrochloride extended-release tablets may cause serious side effects, including:

- See **"What is the most important information I should know about methylphenidate hydrochloride extended-release tablets?"**
- **Painful and prolonged erections (priapism).** Priapism that may require surgery has happened in males who take products that contain methylphenidate. **If you or your child develop priapism, get medical help right away.**
- **Circulation problems in fingers and toes (peripheral vasculopathy, including Raynaud's phenomenon).** Signs and symptoms may include:
  - fingers or toes may feel numb, cool, painful
  - fingers or toes may change color from pale, to blue, to red

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

  Call your healthcare provider right away if you or your child have any signs of unexplained wounds appearing on fingers or toes during treatment with methylphenidate hydrochloride extended-release tablets.
- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with methylphenidate hydrochloride extended-release tablets. Methylphenidate hydrochloride extended-release tablets treatment may be stopped if your child is not growing or gaining weight as expected.
- **Risk of intestinal blockage in people with narrowed digestive tract (gastrointestinal narrowing).** Because the methylphenidate hydrochloride extended-release tablet does not change in shape in the intestines (GI tract), methylphenidate hydrochloride extended-release tablets should not be taken by people with severe intestinal problems (pre-existing severe gastrointestinal narrowing).
- **Eye problems (increased pressure in the eye and glaucoma).** Call your healthcare provider right away if you or your child develop changes in your vision or eye pain, swelling, or redness.
- **New or worsening tics or worsening Tourette's syndrome.** Tell your healthcare provider if you or your child get any new or worsening tics or worsening Tourette's syndrome during treatment with methylphenidate hydrochloride extended-release tablets.
- **Eyesight changes or blurred vision.**
- **Possible blockage of the intestine.** Because the methylphenidate hydrochloride extended-release tablets do

not change in shape in the intestines (GI tract), methylphenidate hydrochloride extended-release tablets should not be taken by people with severe intestinal problems (pre-existing severe gastrointestinal narrowing).

The most common side effect of methylphenidate hydrochloride extended-release tablets in children 6 to 17 years of age is upper stomach-area (abdominal) pain.

The most common side effect of methylphenidate hydrochloride extended-release tablets in adults up to 65 years of age include:

- decreased appetite
- headache
- dry mouth
- nausea
- trouble sleeping
- anxiety
- dizziness
- weight loss
- irritability
- fast heart beat
- increased sweating

These are not all the possible side effects of methylphenidate hydrochloride extended-release tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Trigen Laboratories, LLC at 1-800-444-5164.

How should I store methylphenidate hydrochloride extended-release tablets?

- Store methylphenidate hydrochloride extended-release tablets at room temperature between 59°F to 86°F (15°C to 30°C).
- Protect from moisture.
- Store methylphenidate hydrochloride extended-release tablets in a safe place, like a locked cabinet.
- Dispose of remaining, unused, or expired methylphenidate hydrochloride extended-release tablets by a medicine take-back program at a U.S. Drug Enforcement Administration (DEA) authorized collection site. If no take-back program or (DEA) authorized collector is available, mix methylphenidate hydrochloride extended-release tablets with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away methylphenidate hydrochloride extended-release tablets in the household trash. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Keep methylphenidate hydrochloride extended-release tablets and all medicines out of the reach of children.

General information about the safe and effective use of methylphenidate hydrochloride extended-release tablets.

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

You can ask your pharmacist or healthcare provider for information about methylphenidate hydrochloride extended-release tablets that is written for health professionals.

What are the ingredients in methylphenidate hydrochloride extended-release tablets?

Active ingredient: methylphenidate hydrochloride

Inactive ingredients: black iron oxide, cellulose acetate, colloidal silicon dioxide, ferrosoferric oxide, hypromellose, lactose monohydrate, magnesium stearate, phosphoric acid, polyethylene glycol, polyethylene

oxide, sodium chloride, succinic acid, titanium dioxide, triacetin. In addition,

18 mg tablets contain: iron oxide red, iron oxide yellow

27 mg tablets contain: FD&C Yellow #6 Aluminum Lake, FD&C Blue #2 Aluminum Lake, FD&C Red #40 Aluminum Lake

54 mg tablets contain: FD&C Yellow #6 Aluminum Lake, FD&C Red #40 Aluminum Lake, FD&C Blue #2 Aluminum Lake

72 mg tablets contain: FD&C Blue #1 Aluminum Lake

Manufactured for:
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