Methylphenidate HCl extended-release tablets CII

200320-1 Rev. 06/2022

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

----------INDICATIONS AND USAGE----------
Methylphenidate hydrochloride 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)

------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------
- Serious Cardiovascular Reactions: Sudden death has been reported in association with CNS stimulant treatment at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias or coronary artery disease. (5.2)
- Blood Pressure and Heart Rate Increases: Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic. (5.3)
- Psychiatric Adverse Reactions: Use of stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with preexisting psychiatric illness. Evaluate for bipolar prior to methylphenidate hydrochloride extended-release tablets use. Monitor for aggressive behavior. (5.4)
- Priapism: Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of painful or prolonged penile erections or priapism are observed. (5.4)
- Peripheral Vasculopathy, including Raynaud's Phenomenon: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.5)
- Long-Term Suppression of Growth: monitor height and weight at appropriate intervals in pediatric patients. (5.6)
- Gastrointestinal Obstruction: Avoid use with preexisting GI narrowing. (5.8)

----------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.

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

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

1 INDICATIONS AND USAGE

Methylphenidate hydrochloride 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)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to initiating treatment 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)]*.

Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy. Maintain careful prescription records, educate patients about abuse, and periodically re-evaluate the need for methylphenidate hydrochloride extended-release tablets use *[see Boxed Warning, Warning and Precautions (5.1), Drug Abuse andDependence (9)]*.

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

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

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 Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse effects 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 Potential for Abuse and Dependence

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

5.2 Serious Cardiovascular Reactions

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

5.3 Blood Pressure and Heart Rate Increases

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)]*. Individuals may have larger increases. Monitor all patients for hypertension and tachycardia.

5.4 Psychiatric Adverse Reactions

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

5.5 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products, including another formulation of methylphenidate hydrochloride extended-release tablets, in both pediatric and adult patients *[see Adverse Reactions (6.2)]*. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

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

5.7 Long-Term Suppression of Growth

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

Careful follow-up of weight and height in 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 consistently medicated pediatric patients (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about
2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

Closely monitor growth (weight and height) in pediatric patients treated with stimulants, including methylphenidate hydrochloride extended-release tablets. 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)]*.

6 ADVERSE REACTIONS

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

- Abuse and Dependence *[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)]*
- Serious Cardiovascular Reactions *[see Warnings and Precautions (5.2)]*
- Blood Pressure and Heart Rate Increases *[see Warnings and Precautions (5.3)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Priapism *[see Warnings and Precautions (5.5)]*
- Peripheral Vasculopathy, including Raynaud's Phenomenon *[see Warnings and Precautions (5.6)]*
- Long-Term Suppression of Growth *[see Warnings and Precautions (5.7)]*
- Potential for Gastrointestinal Obstruction *[see Warnings and Precautions (5.8)]*

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 Tablet: (n=423) %	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	4.1
Anxiety	8.2	2.4
Initial insomnia	4.3	2.8
Depressed mood	3.8	1.4
Nervousness	3.1	0.5
Restlessness	3.1	0
Agitation	2.2	0.5
Aggression	1.7	0.5
Tension	1.7	0.5
Depression	1.7	0.9
Libido decreased	1.7	0.5
Affect labile	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 8 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, 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

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 for the treatment of ADHD have been established in pediatric patients 6 to 17 years.

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 can cause serious side effects, including:

- **Abuse and dependence.** Methylphenidate hydrochloride extended-release tablets, other methylphenidate containing medicines, and amphetamines have a high chance for abuse and can cause physical and psychological dependence. Your healthcare provider should check you or your child for signs of abuse and dependence before and during treatment with methylphenidate hydrochloride extended-release tablets.
  - Tell your healthcare provider if you or your child has ever abused or been dependent on alcohol, prescription medicines, or street drugs.
  - Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.
- **Heart-related problems, including:**
  - sudden death, stroke, and heart attack in adults
  - sudden

- 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.
- Your healthcare provider may sometimes stop methylphenidate hydrochloride extended-release tablets treatment for a while to check ADHD symptoms.

If you or your child take too much methylphenidate hydrochloride extended-release tablets, call your healthcare provider or poison control center 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 can 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).

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 authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or authorized collector is available, mix 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.

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 was 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

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

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

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

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

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

CNS stimulants, including methylphenidate hydrochloride extended-release tablets, other methylphenidate-containing products, and amphetamines have a high potential for abuse. Abuse is the intentional, non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. 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. Both abuse and misuse may lead to addiction, and some individuals may develop addiction even when taking methylphenidate hydrochloride extended-release tablets as prescribed.

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

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

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 from continued therapy. Physical dependence is a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants 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 from continued therapy. Tolerance is a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time.

10 OVERDOSAGE

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

Management of Overdose
Provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdosage. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.

Consider contacting a Poison Center (1-800-222-1222) or a medical toxicologist for additional 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 25.5°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

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

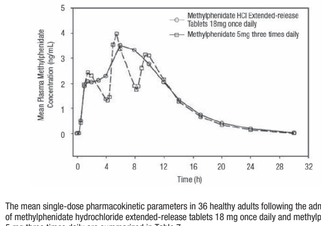
In a relative bioavailability study in healthy adults under fasted conditions, plasma exposures of 72 mg methylphenidate hydrochloride extended-release tablets and 72 mg (2 x 36 mg) methylphenidate extended-release tablets were compared. The peak plasma concentration (C_{max}) of 72 mg methylphenidate 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-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

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
$t_{1/2}$ (h)	3.3 ± 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_{tau} 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.

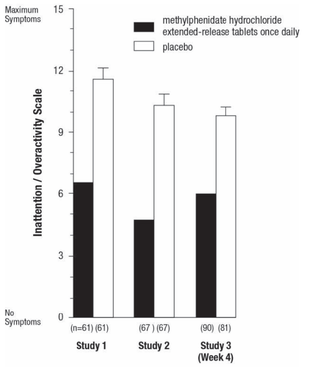
Pediatric Patients 6 to 12 Years

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.

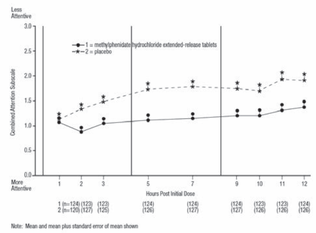
The scores for methylphenidate hydrochloride extended-release tablets and placebo for the three studies are presented in Figure 2. Error bars represent the mean plus standard error of the mean.

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)



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.

Disposal

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

17 PATIENT COUNSELING INFORMATION

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

Controlled Substance Status/High Potential for Abuse and Dependence

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

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)]*.

Serious Cardiovascular Risks

Advise patients, caregivers, and their family members that there is a potential serious cardiovascular risk including sudden death, myocardial infarction, and stroke 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)]*.

Blood Pressure and Heart Rate Increases

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 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 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 (5.5)]*.

- 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.

Suppression of Growth

Advise patients, families and caregivers that methylphenidate hydrochloride extended-release tablets may cause slowing of growth and weight loss *[see Warnings and Precautions (5.6)]*.

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: