Open Size: 17.25 x 18.75 Inch
Close Size: 1.375 x 1.375 Inch (Gluing)
Paper: 40 GSM Bible

17.25”

1.375” 1.375”

1.375”

5.00 mm 5.00 mm

2D Code Area 10x10mm

5250809
METHYLPHENIDATE HYDROCHLORIDE
EXTENDED-RELEASE TABLETS

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 ---

Boxed Warning	10/2023
Indications and Usage (1)	10/2023
Dosage and Administration (2.1, 2.6)	10/2023
Dosage and Administration, Maintenance/Extended Treatment (2.5) Removed	10/2023
Contraindications (4)	10/2023
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.6, 5.7, 5.8, 5.11, 5.12, 5.13)	10/2023
Warnings and Precautions (5.7) Removed	10/2023

--- INDICATIONS AND USAGE ---

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

-- DOSAGE AND ADMINISTRATION --

- Methylphenidate hydrochloride extended-release tablets should be taken once daily in the morning and swallowed whole with the aid of liquids. Methylphenidate hydrochloride extended-release tablets should not be chewed or crushed. Methylphenidate hydrochloride extended-release tablets may be taken with or without food. (2.2)
- For children and adolescents new to methylphenidate, the recommended starting dosage is 18 mg once daily. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed 54 mg/day in children and 72 mg/day in adolescents. (2.3)
- For adult patients new to methylphenidate, the recommended starting dose is 18 or 36 mg/day. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed 72 mg/day for adults. (2.3)
- For patients currently using methylphenidate, dosing is based on current dose regimen and clinical judgment. (2.4)

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

Tablets: 72 mg (3)

-- CONTRAINDICATIONS --

- Known hypersensitivity to the product (4.1)
- Do not use methylphenidate hydrochloride extended-release tablets in patients currently using or within 2 weeks of using an MAO inhibitor (4.2)

--- WARNINGS AND PRECAUTIONS ---

- Risks to Patients with Serious Cardiac Disease: Avoid in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac disease. (5.2)
- Increase in 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)
- Seizures: Stimulants may lower the convulsive threshold. Discontinue in the presence of seizures. (5.5)
- Priapism: If abnormally sustained or frequent and painful erections occur, patients should seek immediate medical attention (5.6)
- 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 (5.7)
- 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 treatment interrupted. (5.8)
- Gastrointestinal obstruction with preexisting GI narrowing. (5.9)
- Hematologic monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy. (5.10)
- 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. (5.11)
- Increased Intraocular Pressure 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. (5.12)
- 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. (5.13)

-- ADVERSE REACTIONS --

The most common adverse reaction in double-blind clinical trials (>5%) in children and adolescents was abdominal pain upper. The most common adverse reactions in double-blind clinical trials (>5%) in adult patients were decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, and hyperhidrosis. (6.1 and 6.2)

The most common adverse reactions associated with discontinuation (≥1%) from either pediatric or adult clinical trials were anxiety, irritability, insomnia, and blood pressure increased. (6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-406-7984 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-- DRUG INTERACTIONS --

- Methylphenidate hydrochloride extended-release tablets may increase blood pressure; use cautiously with vasopressors (7.2)
- Inhibition of metabolism of coumarin anticoagulants, anticonvulsants, and some antidepressants (7.3)

--- 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: 01/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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 children 6 years of age and older, adolescents, and adults up to the age of 65 *[see Clinical Studies (14)]*.

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 (5.13)]*.

2.2 Recommended Dosage

Methylphenidate hydrochloride extended-release tablets should be administered orally once daily in the morning with or without food.

Methylphenidate hydrochloride extended-release tablets must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed *[see Patient Counseling Information (17)]*.

2.3 Patients New to Methylphenidate

The recommended starting dose of methylphenidate hydrochloride extended-release tablets for patients who are not currently taking methylphenidate or stimulants other than methylphenidate is 18 mg once daily for children and adolescents and 18 or 36 mg once daily for adults (see Table 1).

Table 1. Methylphenidate Hydrochloride Extended-Release Tablets Recommended Starting Doses and Dose Ranges

Patient Age	Recommended Starting Dose	Dose Range
Children 6 - 12 years of age	18 mg/day	18 mg - 54 mg/day
Adolescents 13 - 17 years of age	18 mg/day not to exceed 2 mg/kg/day	18 mg - 72 mg/day
Adults 18 - 65 years of age	18 or 36 mg/day	18 mg - 72 mg/day

2.4 Patients Currently Using Methylphenidate

The recommended dose of methylphenidate hydrochloride extended-release tablets for patients who are currently taking methylphenidate twice daily or three times daily at doses of 10 to 60 mg/day is provided in Table 2. Dosing recommendations are based on current dose regimen and clinical judgment. Conversion dosage should not exceed 72 mg daily.

Table 2. Recommended Dose Conversion from Methylphenidate Regimens to Methylphenidate Hydrochloride Extended-Release Tablets

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

Other methylphenidate regimens: Clinical judgment should be used when selecting the starting dose.

2.5 Dose Titration

Doses may be increased in 18 mg increments at weekly intervals for patients who have not achieved an optimal response at a lower dose. Daily dosages above 54 mg in children and 72 mg in adolescents have not been studied and are not recommended. Daily dosages above 72 mg in adults are not recommended.

A 27 mg dosage strength is available for physicians who wish to prescribe between the 18 mg and 36 mg dosages.

2.6 Dosage Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse reactions occur, reduce 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, USP 72 mg are round, biconvex, light blue to blue colored, film-coated tablets, imprinted with “72”, with the presence of an orifice.

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Methylphenidate

Hypersensitivity reactions, such as angioedema and anaphylactic reactions, have been observed in patients treated with methylphenidate hydrochloride extended-release tablets. Therefore, methylphenidate hydrochloride extended-release tablets are contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product *[see Adverse Reactions (6.5)]*.

4.2 Monoamine Oxidase Inhibitors

Methylphenidate hydrochloride extended-release tablets are contraindicated during treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a MAO inhibitor (hypertensive crises may result) *[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)]*. 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 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 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). 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 pre-existing 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 or a family history of suicide, bipolar disorder, or 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 with 0% of placebo-treated patients. If such symptoms occur, consider discontinuing methylphenidate hydrochloride extended-release tablets.

5.5 Seizures

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

5.6 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate use in both adult and pediatric male patients *[see Adverse Reactions (6.5)]*. 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 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.

5.7 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. 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 dosages of CNS stimulants in all age groups throughout the course of treatment. Signs and symptoms generally improved after dosage 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.

5.8 Long-Term Suppression of Growth in Pediatric Patients

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

Careful follow-up of weight and height in children 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 children 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.

5.9 Potential for Gastrointestinal Obstruction

Because the methylphenidate hydrochloride extended-release tablets are nondeformable and do 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 controlled-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)]*.

5.10 Hematologic Monitoring

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

5.11 Acute Angle Closure Glaucoma

There have been rare 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.

5.12 Increased Intraocular Pressure and Glaucoma

There have been reports of an elevation of intraocular pressure (IOP) associated with methylphenidate treatment *[see Adverse Reactions (6.5)]*.

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.

5.13 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 (6.2, 6.5)]*. Worsening of Tourette’s syndrome has also been reported.

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 Boxed Warning, Warnings and Precautions (5.1)]*
- Hypersensitivity to Methylphenidate *[see Contraindications (4.1)]*
- Monoamine Oxidase Inhibitors *[see Contraindications (4.2) 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)]*
- Seizures *[see Warnings and Precautions (5.5)]*
- Priapism *[see Warnings and Precautions (5.6)]*
- Peripheral Vasculopathy, including Raynaud’s Phenomenon *[see Warnings and Precautions (5.7)]*
- Long-Term Suppression of Growth in Pediatric Patients *[see Warnings and Precautions (5.8)]*
- Potential for Gastrointestinal Obstruction *[see Warnings and Precautions (5.9)]*
- Hematologic Monitoring *[see Warnings and Precautions (5.10)]*
- Acute Angle Closure Glaucoma *[see Warnings and Precautions (5.11)]*
- Increased Intraocular Pressure and Glaucoma *[see Warnings and Precautions (5.12)]*
- Motor and Verbal Tics, and Worsening of Tourette’s Syndrome *[see Warnings and Precautions (5.13)]*

The most common adverse reaction in double-blind clinical trials (>5%) in pediatric patients (children and adolescents) was abdominal pain upper. The most common adverse reactions in double-blind clinical trials (>5%) in adult patients were decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, and hyperhidrosis *[see Adverse Reactions (6.1)]*.

The most common adverse reactions associated with discontinuation (≥1%) from either pediatric or adult clinical trials were anxiety, irritability, insomnia, and blood pressure increased *[see Adverse Reactions (6.3)]*.

The development program for methylphenidate hydrochloride extended-release tablets included exposures in a total of 3906 participants in clinical trials. Children, adolescents, and adults with ADHD were evaluated in 6 controlled clinical studies and 11 open-label clinical studies (see Table 3). Safety was assessed by collecting adverse events, vital signs, weights, and ECGs, and by performing physical examinations and laboratory analyses.

Table 3. Methylphenidate Hydrochloride Extended-Release Tablets Exposure in Double-Blind and Open-Label Clinical Studies

Patient Population	N	Dose Range
Children	2216	18 to 54 mg once daily
Adolescents	502	18 to 72 mg once daily
Adults	1188	18 to 108 mg once daily

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

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

Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of methylphenidate hydrochloride extended-release tablets based on the comprehensive assessment of the available adverse event information. A causal association for methylphenidate hydrochloride extended-release tablets often cannot be reliably established in individual cases. Further, 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 majority of adverse reactions were mild to moderate in severity.

6.1 Commonly Observed 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.

Children and Adolescents

Table 4 lists the adverse reactions reported in 1% or more of methylphenidate hydrochloride extended-release tablets-treated children and adolescent subjects in 4 placebo-controlled, double-blind clinical trials.

Table 4. Adverse Reactions Reported by ≥1% of Methylphenidate Hydrochloride Extended-Release Tablets-Treated Children and Adolescent Subjects in 4 Placebo-Controlled, Double-Blind Clinical Trials of Methylphenidate Hydrochloride Extended-Release Tablets

System/Organ Class Adverse Reaction	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.

The majority of adverse reactions were mild to moderate in severity.

Adults

Table 5 lists the adverse reactions reported in 1% or more of methylphenidate hydrochloride extended-release tablets-treated adults in 2 placebo-controlled, double-blind clinical trials.

Table 5. Adverse Reactions Reported by ≥1% of Methylphenidate Hydrochloride Extended-Release Tablets-Treated Adult Subjects in 2 Placebo-Controlled, Double-Blind Clinical Trials*

System/Organ Class Adverse Reaction	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.

The majority of ADRs were mild to moderate in severity.

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

This section includes adverse reactions reported by methylphenidate hydrochloride-treated subjects in double-blind trials that do not meet the criteria specified for Table 4 or Table 5 and all adverse reactions reported by methylphenidate hydrochloride extended-release tablets-treated subjects 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

6.3 Discontinuation Due to Adverse Reactions

Adverse reactions in the 4 placebo-controlled studies of children and adolescents leading to discontinuation occurred in 2 methylphenidate hydrochloride extended-release tablets patients (0.6%) 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 2 placebo-controlled studies of adults, 25 methylphenidate hydrochloride extended-release tablets patients (6.0%) and 6 placebo patients (2.8%) discontinued due to an adverse reaction. Those events with an incidence of >0.5% in the methylphenidate hydrochloride extended-release tablets patients 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 11 open-label studies of children, adolescents, and adults, 266 methylphenidate hydrochloride extended-release tablets patients (7.0%) discontinued due to an adverse reaction. Those events with an incidence of >0.5% included insomnia (1.2%), irritability (0.8%), anxiety (0.7%), decreased appetite (0.7%), and tic (0.6%).

6.4 Blood Pressure and Heart Rate Increases

In the laboratory classroom clinical trials in children (Studies 1 and 2), both 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 adolescent trial (Study 4), 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, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase 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 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 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 methylphenidate hydrochloride

Dispense with Medication Guide available at: www.sunpharma.com/usa/products

MEDICATION GUIDE
Methylphenidate Hydrochloride Extended-Release Tablets, USP, for oral use, CII
(meth" əl-fen 'i-dāt)

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.

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 and Hyperactivity Disorder (ADHD) in children 6 years of age and older and adults up to 65 years of age. Methylphenidate hydrochloride extended-release tablets may help increase attention and decrease impulsiveness and hyperactivity in people with ADHD.

It is not known if methylphenidate hydrochloride extended-release tablets are safe and effective in children under 6 years of age.

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 they contain 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 they 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.
- are taking, or have stopped taking within the past 14 days, a medicine called 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 or have had seizures or have had an abnormal brain wave test (EEG)
- 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.
- are breastfeeding or plan to breastfeed. It is not known if methylphenidate hydrochloride passes into the breastmilk. 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 take:

- a medicine to treat blood pressure
- coumarin anticoagulants (a medicine that prevent blood clots, such as warfarin)
- a medicine to treat seizures
- a medicine to treat depression
- 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 methylphenidate hydrochloride extended-release tablets be taken?

- 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.

18.75”

Open Size : 17.25 x 18.75 inch
Close Size ; 1.375 x 1.375 inch
Color : Black
Track : A04/01/2024-II, A09/01/2024, A19/01/2024, A17/04/2024, A30/04/2024, A07/05/2024

- 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 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.
- Your healthcare provider may do blood tests during treatment with methylphenidate hydrochloride extended-release tablets to check your or your child's blood count.

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?"**
- **Seizures.** Your healthcare provider will stop treatment with methylphenidate hydrochloride extended-release tablets if you or your child have a seizure.
- **Painful and prolonged erections (priapism).** Priapism that may require surgery has happened in people 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.
- **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 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 effect of methylphenidate hydrochloride extended-release tablets in children is upper stomach-area (abdominal) pain.

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

- decreased appetite
- headache
- dry mouth
- nausea
- trouble sleeping
- anxiety
- dizziness
- weight loss
- irritability
- 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 Sun Pharmaceutical Industries, Inc. at 1-800-406-7984.

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 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 HCl, USP

Inactive Ingredients: cellulose acetate, colloidal silicon dioxide, FD&C Blue No. 1, FD&C Red No. 40 Aluminum Lake, hypromellose, lactose monohydrate, phosphoric acid, polyethylene glycol, polyethylene oxide, povidone, sodium chloride, stearic acid, succinic acid, talc, titanium dioxide and triacetin.

The printing ink also contains: black iron oxide, and shellac glaze.

Manufactured by:
Ohm Laboratories Inc.
New Brunswick, NJ 08901

Distributed by:
Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512

For more information call 1-800-406-7984

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

Revised: 01/2024

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 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 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)]*.

6.5 Postmarketing Experience

The following additional adverse reactions have been identified during postapproval 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, 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 MAO Inhibitors

Methylphenidate hydrochloride extended-release tablets should not be used in patients being treated (currently or within the preceding 2 weeks) with MAO inhibitors *[see Contraindications (4.2)]*.

7.2 Vasopressor Agents

Because of possible increases in blood pressure, methylphenidate hydrochloride extended-release tablets should be used cautiously with vasopressor agents *[see Warnings and Precautions (5.3)]*.

7.3 Coumarin Anticoagulants, Antidepressants, and Selective Serotonin Reuptake Inhibitors

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

7.4 Halogenated Anesthetics

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. Monitor blood pressure and avoid use of methylphenidate hydrochloride extended-release tablets in patients being treated with anesthetics on the day of surgery.

7.5 Risperidone

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). Monitor for signs of EPS.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and 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 15-fold and 3-fold the maximum recommended human dose of methylphenidate hydrochloride extended-release tablets on a mg/kg and mg/m^2 basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPAA in pregnant rats was 1-2 times that seen in trials in volunteers and patients with the maximum recommended dose of methylphenidate hydrochloride based on the AUC.

The safety of methylphenidate for use during human pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. Methylphenidate hydrochloride extended-release tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of methylphenidate hydrochloride on labor and delivery in humans is unknown.

8.3 Nursing Mothers

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

In lactating female rats treated with a single oral dose of 5 mg/kg radiolabeled methylphenidate, radioactivity (representing methylphenidate and/or its metabolites) was observed in milk and levels were generally similar to those in plasma.

8.4 Pediatric Use

Methylphenidate hydrochloride extended-release tablets should not be used in children under six years, since safety and efficacy in this age group have not been established. Long-term effects of methylphenidate in children have not been well established.

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 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 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 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 methylphenidate hydrochloride extended-release tablets (108 mg) 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, 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 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 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 22% of the total amount of methylphenidate in methylphenidate hydrochloride extended-release tablets is available for immediate release from the drug overcoat *[see System Components and Performance (11.1)]*.

Although these findings reveal a relatively lower response to 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 at a lower dose).

10 OVERDOSAGE

10.1 Clinical Effects of Overdose

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

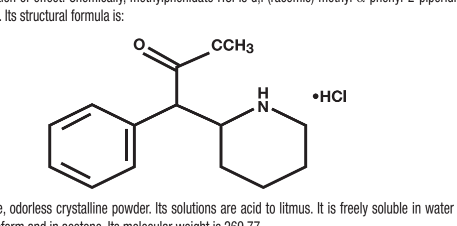
- Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden cardiac death. Takotsubo cardiomyopathy may develop.
- CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin 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 are available in one tablet strength. Each extended-release tablet for once-a-day oral administration contains 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 molecular 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 contain the following inactive ingredients: cellulose acetate, colloidal silicon dioxide, FD&C Blue No. 1, FD&C Red No. 40 Aluminum Lake, hypromellose, lactose monohydrate, phosphoric acid, polyethylene glycol, polyethylene oxide, povidone, sodium chloride, stearic acid, succinic acid, talc, titanium dioxide and triacetin.

The printing ink also contains: black iron oxide, and shellac glaze.

This product meets USP dissolution test 2.

11.1 System Components and Performance

Methylphenidate hydrochloride extended-release tablets uses 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 HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

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.

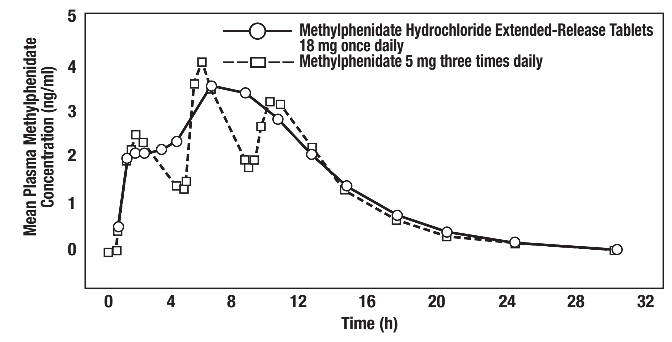
12.3 Pharmacokinetics

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 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). The relative bioavailability of methylphenidate hydrochloride extended-release tablets once daily and methylphenidate three times daily in adults is comparable.

Figure 1. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of methylphenidate hydrochloride extended-release tablets 18 mg once daily and immediate-release methylphenidate 5 mg three times daily administered every 4 hours.



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 6.

Table 6. 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/day. 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 $t_{½}$ 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 to 144 mg.

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 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 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 in adolescent ADHD patients aged 13 to 16 administered their prescribed dose (18 to 72 mg/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 adolescents 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.

Metabolism and Excretion

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.

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.

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. There is no evidence of dose dumping in the presence or absence of food.

Alcohol Effect

An *in vitro* study was conducted to explore the effect of alcohol on the release characteristics of methylphenidate from the methylphenidate hydrochloride extended-release 18 mg tablet dosage form. At an alcohol concentration up to 40% there was no increased release of methylphenidate in the first hour. The results with the 18 mg tablet strength are considered representative of the other available tablet strengths.

Special Populations

Gender

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.

Race

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.

Age

Increase in age resulted in increased apparent oral clearance (CL/F) (58% increase in adolescents compared to children). 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 children less than 6 years of age.

Renal Insufficiency

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.

Hepatic Insufficiency

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

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

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

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 80-fold and 8-fold the highest recommended human dose of methylphenidate hydrochloride extended-release tablets on a mg/kg and mg/m^2 basis, respectively.

14 CLINICAL STUDIES

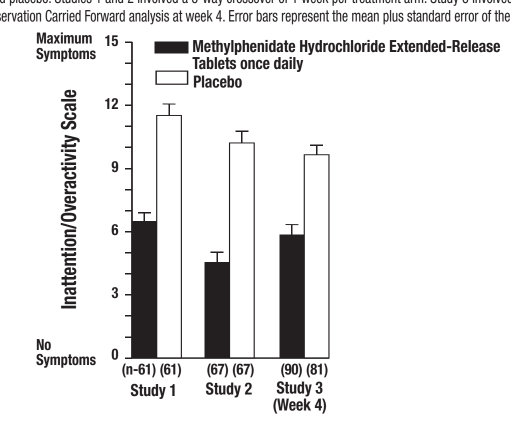
Methylphenidate hydrochloride extended-release tablets were demonstrated to be effective in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in 4 randomized, double-blind, placebo-controlled studies in children and adolescents and 2 double-blind placebo-controlled studies in adults who met the Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD.

14.1 Children

Three double-blind, active- and placebo-controlled studies were conducted in 416 children aged 6 to 12 years. The controlled studies compared methylphenidate hydrochloride extended-release tablets given once daily (18, 36, or 54 mg), methylphenidate given three times daily over 12 hours (15, 30, 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. The scores for methylphenidate hydrochloride extended-release tablets and placebo for the three studies are presented in Figure 2.

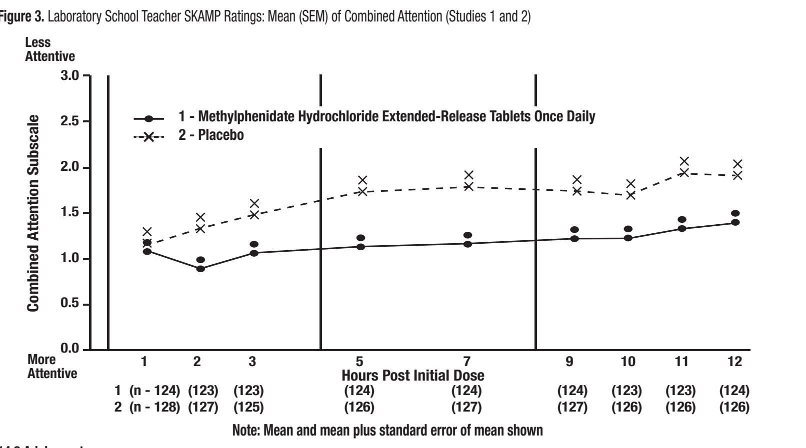
Figure 2. Mean Community School Teacher IOWA Conners Inattention/Overactivity Scores with methylphenidate hydrochloride extended-release tablets once daily (18, 36, or 54 mg) and placebo. Studies 1 and 2 involved a 3-way crossover of 1 week per treatment arm. Study 3 involved 4 weeks of parallel-group 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 were evaluated by laboratory schoolteachers using the 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.

*Swanson, Kotkin, Agler, M-Fynn, and Pelham

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



14.2 Adolescents

In a randomized, double-blind, multicenter, placebo-controlled trial (Study 4) involving 177 patients, methylphenidate hydrochloride extended-release tablets were demonstrated to be effective in the treatment of ADHD in adolescents aged 13 to 18 years at doses up to 72 mg/day (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/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 dose 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 this phase, mean scores for the investigator rating on the ADHD Rating Scale demonstrated that methylphenidate hydrochloride extended-release tablets were statistically significantly superior to placebo.

14.3 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 to 108 mg/day) and in a multicenter, parallel-group, 5-week, fixed-dose study (Study 6) (18, 36, and 72 mg/day).

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/day to 108 mg/day 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/day and patients continued with incremental increases of 18 mg/day (36 to 108 mg/day) 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 that methylphenidate hydrochloride extended-release tablets were 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, 36, 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/day (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

Methylphenidate hydrochloride extended-release tablets, USP are available in the 72 mg strength, as round, biconvex, light blue to blue colored, film-coated tablets, imprinted with "72", with the presence of an orifice.

The tablets are supplied as follows:

Bottles of 30 NDC 57664-710-83
Bottles of 100 NDC 57664-710-88

Storage and Handling

Dispense in a tight, light-resistant container as defined in the USP with a child-resistant closure.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from moisture and 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), 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 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 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 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 (5.6)]*.

Circulation Problems in Fingers and Toes [Peripheral Vasculopathy, including Raynaud's Phenomenon]

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 physician 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, caregivers, and family members that methylphenidate hydrochloride extended-release tablets may cause slowing of growth and weight loss *[see Warnings and Precautions (5.8)]*.

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 (5.12)]*.

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 (5.13)]*.

Administration Instructions

Patients should be informed that methylphenidate hydrochloride extended-release tablets should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. 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; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

For more information, call Sun Pharmaceutical Industries, Inc. at 1-800-406-7984.

Dispense with Medication Guide available at: www.sunpharma.com/usa/products

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