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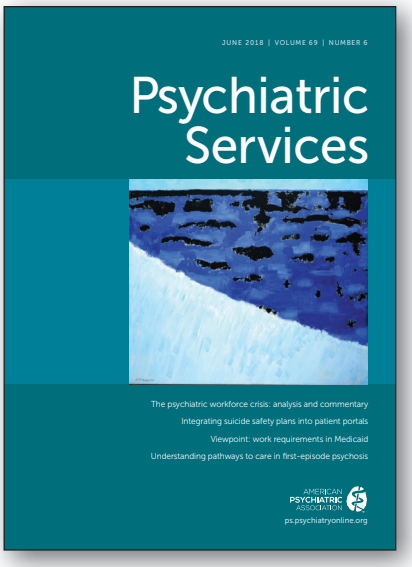

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Methylphenidate hydrochloride extended-release tablets USP, for oral use CII

BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

WARNING: DRUG DEPENDENCE
See full prescribing information for complete boxed warning.
Methylphenidate hydrochloride extended-release tablets should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior.

INDICATIONS AND USAGE

Methylphenidate hydrochloride extended-release tablets USP is 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.

CONTRAINDICATIONS

Known hypersensitivity to the product. Marked anxiety, tension, or agitation. Glaucoma. Tics or a family history or diagnosis of Tourette's syndrome. Do not use methylphenidate hydrochloride extended-release tablets in patients currently using or within 2 weeks of using an MAO inhibitor.

WARNINGS AND PRECAUTIONS

Serious Cardiovascular Events: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems.

Increase in Blood Pressure: Monitor patients for changes in heart rate and blood pressure and use with caution in patients for whom an increase in blood pressure or heart rate would be problematic.

Psychiatric Adverse Events: 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. Clinical evaluation for Bipolar Disorder is recommended prior to stimulant use. Monitor for aggressive behavior.

Seizures: Stimulants may lower the convulsive threshold. Discontinue in the presence of seizures.

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.

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.

Visual Disturbance: difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

Long-Term Suppression of Growth: monitor height and weight at appropriate intervals in pediatric patients.

Gastrointestinal obstruction with preexisting GI narrowing.

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

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.

The most common adverse reactions associated with discontinuation (≥1%) from either pediatric or adult clinical trials were anxiety, irritability, insomnia, and blood pressure increased. 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. Safety was assessed by collecting adverse events, vital signs, weights, and ECGs, and by performing physical examinations and laboratory analyses.

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

Adverse Reactions Reported by ≥1% of methylphenidate hydrochloride extended-release tablets-Treated Children and Adolescent Subjects

4 Placebo-Controlled, Double-Blind Clinical Trials of methylphenidate hydrochloride extended-release tablets – methylphenidate hydrochloride extended-release tablets (n=321), Placebo (n=318): Abdominal pain upper (6.2, 3.8), Vomiting (2.8, 1.6), Nasopharyngitis (2.8, 2.2), Pyrexia (2.2, 0.9), Insomnia* (2.8, 0.3), Cough (1.9, 0.9), Dizziness (1.9, 0), 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.

Adverse Reactions Reported by ≥1% of methylphenidate hydrochloride extended-release tablets-Treated Adult Subjects

2 Placebo-Controlled, Double-Blind Clinical Trials* – methylphenidate hydrochloride extended-release tablets (n=415), Placebo (n=212):

Decreased appetite (25.3, 6.6), Headache (22.2, 15.6), Dry mouth (14.0, 3.8), Nausea (12.8, 3.3), Insomnia (12.3, 6.1), Anxiety (8.2, 2.4), Dizziness (6.7, 5.2), Weight decreased (6.5, 3.3), Irritability (5.8, 1.4), Hyperhidrosis (5.1, 0.9), Tachycardia (4.8, 0), Initial insomnia (4.3, 2.8), Depressed mood (3.9, 1.4), Nervousness (3.1, 0.5), Palpitations (3.1, 0.9), Restlessness (3.1, 0), Tremor (2.7, 0.5), Dyspepsia (2.2, 0.9), Agitation (2.2, 0.5), Upper respiratory tract infection (2.2, 0.9), Muscle tightness (1.9, 0), Vertigo (1.7, 0), Vision blurred (1.7, 0.5), Vomiting (1.7, 0.5), Anorexia (1.7, 0), Aggression (1.7, 0.5), Bruxism (1.7, 0.5), Depression (1.7, 0.9), Libido decreased (1.7, 0.5), Oropharyngeal pain (1.7, 1.4), Affect lability (1.4, 0.9), Constipation (1.4, 0.9), Paresthesia (1.2, 0), Sedation (1.2, 0), Tension headache (1.2, 0.5), Confusional state (1.2, 0), Tension (1.2, 0.5)

*Included doses up to 108 mg.

The majority of ADRs were mild to moderate in severity for children, adolescents and adult subjects.

DRUG INTERACTIONS

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.

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.

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.

USE IN SPECIFIC POPULATIONS

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 extended-release tablets 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.

Labor and Delivery

The effect of methylphenidate hydrochloride extended-release tablets on labor and delivery in humans is unknown.

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 is 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.

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.

Geriatric Use

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Methylphenidate is a Schedule II controlled substance under the Controlled Substances Act.

Abuse

As noted in the Box Warning, methylphenidate hydrochloride extended-release tablets should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse.

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.

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.

Dependence

As noted in the Box Warning, careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

OVERDOSAGE

Signs and symptoms of methylphenidate hydrochloride extended-release tablets overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, muscle twitching, convulsion, grand mal convulsion, confusional state, hallucinations (auditory and/or visual), hyperhidrosis, headache, pyrexia, tachycardia, palpitations, heart rate increased, sinus arrhythmia, hypertension, rhabdomyolysis, mydriasis, and dry mouth.

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for pyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for methylphenidate hydrochloride extended-release tablets overdosage has not been established. The prolonged release of methylphenidate from methylphenidate hydrochloride extended-release tablets should be considered when treating patients with overdose.

As with the management of all overdosage, the possibility of multiple-drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

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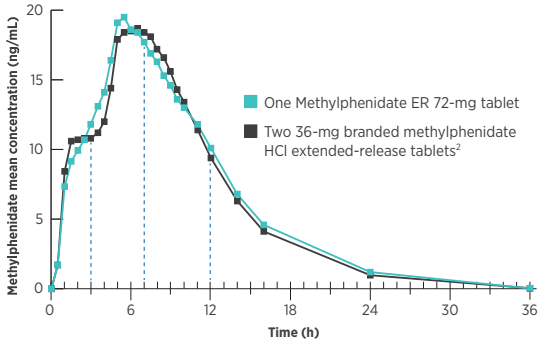

Per revised FDA guidance in 2014, additional bioequivalence metrics are required to ensure that a new methylphenidate ER alternative is therapeutically equivalent to branded methylphenidate HCL extended-release tablets.[3]

Metrics	Meets FDA Bioequivalence Criteria
Cmax	✓
$AUC_{(0-\infty)}$	✓
$AUC_{(0-3)}$	✓
$AUC_{(3-7)}$	✓
$AUC_{(7-12)}$	✓

A single-dose, two-treatment, four-period, two-sequence, fully replicated crossover in-vivo study was conducted in 60 healthy volunteers to compare one Methylphenidate ER 72-mg tablet to two 36-mg branded methylphenidate HCl extended-release tablets.[2]

Indication and Important Safety Information

The 72-mg methylphenidate hydrochloride extended-release tablet USP is a CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adolescents 13 years of age and older, and adults up to the age of 65.

WARNING: DRUG DEPENDENCE

See full prescribing information for complete boxed warning.

Methylphenidate hydrochloride extended-release tablets should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abuse can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior.

- Methylphenidate hydrochloride extended-release tablets should not be used in patients with known hypersensitivity to the product; marked anxiety, tension, or agitation; glaucoma; tics or a family history or diagnosis of Tourette's syndrome; or in patients currently using or within 2 weeks of using an MAO inhibitor
- Methylphenidate is a stimulant. Stimulants should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. Stimulants should be used with caution in patients with a history of high blood pressure or increased heart rate. Patients with a history of high blood pressure and for whom methylphenidate is deemed an appropriate therapy should be monitored for changes in heart rate and blood pressure
- Use of stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior psychiatric history. Stimulants may also exacerbate psychiatric symptoms in patients with preexisting psychiatric illness
- Stimulants may lower the convulsive threshold in patients with epilepsy, potentially leading to seizures. Stimulants should not be taken in the presence of seizures
- Immediate medical attention should be sought if signs or symptoms of prolonged penile erections (priapism) are observed
- Careful observation for peripheral vasculopathy in extremities, including but not limited to Raynaud's phenomenon, is necessary during treatment with ADHD stimulants
- Pediatric patients should be monitored for height and weight at age-appropriate intervals for potential long-term suppression of growth
- Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. Patients with a history of glaucoma should not take stimulants
- This extended-release tablet is nondeformable and does not appreciably change in shape in the GI tract; therefore, gastrointestinal obstruction may potentially occur in patients with prior history of GI narrowing
- Periodic complete blood count (CBC) with differential and platelet counts are advised during prolonged therapy
- The most common adverse reaction in double-blind clinical trials (>5%) in children and adolescents was upper abdominal pain. 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 decrease, irritability, and hyperhidrosis

Please see Important Safety Information above and Brief Summary of Prescribing Information on next page, including **Box Warning**.

References: 1. Methylphenidate hydrochloride extended-release tablets [package insert]. Trigen Laboratories, LLC; 2017. **2.** Data on file. Osmotica Pharmaceutical US LLC. **3.** US Food and Drug Administration. Draft Guidance on Methylphenidate Hydrochloride. Revision: November 2014.

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