Methylphenidate Hydrochloride

**Uses**

Methylphenidate is used alone or combined with behavioral treatment as an adjunct to psychological, educational, social, and other remedial measures in the treatment of ADHD (hyperkinetic disorder, hyperactive syndrome of childhood). ADHD is one of the most prevalent chronic health conditions in school-aged children. Although ADHD has been reported more frequently in boys than in girls, there is a general disconnect between developmental or educational (school) and psychiatric (clinical) settings.Rates of ADHD in the United States vary widely based on factors such as diagnostic criteria used, method of assessment, and study population. In most cases, ADHD becomes apparent (and thus comes to medical attention) during the first few years of grade school. Some impairment from symptoms is present in at least 2 settings (e.g., at home, school, or both). There is a clear trend toward symptomatic improvement in ADHD patients who have received pharmacological treatment. For example, in a study of methylphenidate treatment, children with ADHD who were treated with methylphenidate showed significant improvement in symptoms of inattention, hyperactivity, and impulsivity compared to placebo-controlled trials. In addition, methylphenidate has been shown to improve academic performance, reduce problems in the classroom, and improve quality of life for both children and their families. The long-term effects of methylphenidate treatment are not fully understood, and further research is needed to elucidate the potential risks and benefits of this medication.

**Diagnostic Considerations**

ADHD is one of the most commonly diagnosed neurobehavioral disorders of childhood, generally estimated as occurring in 3-12% of US school-age children, although wider ranges of prevalence have been reported. Within this range, reported prevalence rates generally are higher for boys than girls and for second graders versus school starters at age 6. ADHD is one of the most prevalent chronic health conditions in school-aged children. Although ADHD has been reported more frequently in boys than in girls (ratio of boys to girls varies between 3:1 to 5:1), this difference may be attributable to differences in age at onset and severity of symptoms.

Children with ADHD usually exhibit pronounced difficulties and impairments resulting from the disorder across multiple settings (e.g., school, home, and community). Symptoms include difficulties with attention, hyperactivity, impulsivity, emotional lability, and social-emotional functioning. The diagnosis of ADHD requires the presence of multiple symptoms across different settings and the onset of symptoms before the age of 7 years. In children with ADHD, symptoms often begin in early childhood and continue into adolescence and adulthood. The prevalence of ADHD in children and adolescents is estimated to be as high as 5-10% of the population. ADHD is more common in boys than in girls, with a male-to-female ratio of about 3:1. However, the rate of ADHD in girls has been increasing over the past few decades, and some studies have suggested that girls may be underdiagnosed or misdiagnosed compared to boys.

Impulsivity and hyperactivity in children with ADHD have been associated with poor academic performance, social difficulties, and behavioral problems. Children with ADHD may struggle with controlling impulses, making hasty decisions, and controlling actions in social situations. They may also experience difficulties in regulating their behavior, which can lead to problems in school, home, and community settings. For example, studies have shown that children with ADHD are more likely to engage in disruptive behaviors, such as temper tantrums, aggression, and rule-breaking, compared to children without ADHD.

**Therapeutic Considerations**

Therapeutic considerations for children with ADHD should be based on a comprehensive evaluation of the individual's symptoms, severity, and impact on daily functioning. Treatment decisions should be made in consultation with the child's healthcare provider and should involve taking into account the child's age, gender, and overall medical history. Medications such as methylphenidate and atomoxetine are commonly used to manage the symptoms of ADHD. These medications have been shown to improve symptoms of inattention, hyperactivity, and impulsivity in children with ADHD, although the effects may vary depending on the individual and the specific medication.

Methylphenidate is available in several formulations, including oral tablets, extended-release capsules, and a solution. The oral solution is often preferred for its convenience and ease of administration. Methylphenidate is a centrally acting stimulant that increases levels of dopamine and norepinephrine in the brain, which may help improve attention and decrease impulsivity and hyperactivity. However, there is limited evidence regarding the long-term effects of methylphenidate treatment, and there is a need for further research to understand the potential risks and benefits of this medication. In addition, methylphenidate treatment may be associated with side effects such as headaches, anorexia, and insomnia. These side effects are usually mild and do not require discontinuation of the medication. However, careful monitoring of the patient's response to treatment and regular follow-up visits are essential to ensure safe and effective management of ADHD.

**Therapeutic Considerations: Considerations in Choosing a Therapy**

The choice of therapeutic intervention(s) for ADHD will depend on comorbid conditions, the severity of symptoms, and the preferences of the patient, family, school, and community. Parents, school personnel, and patients should be involved in discussions about treatment options. A wide variety of treatments have been employed for the management of ADHD, including drug therapy with amphetamines and similar stimulants (e.g., methylphenidate, pemisidate), as well as behavioral therapy, cognitive-behavioral therapy, and psychosocial interventions. Several studies have shown that treatments that combine medication and behavioral therapy are more effective than either treatment alone. Current evidence supports the efficacy of stimulants and psychosocial treatment; however, there are no well-designed, long-term studies employing these treatments beyond 14 months nor is there information on long-term outcomes of drug therapy in educational and occupational achievements, involvement with peers, or other areas of social functioning. Results from double-blind controlled studies in 416 children severe than is observed in individuals with a comparable developmental level, and core symptoms include developmentally inappropriate levels of attention and concentration, activity, distractibility, and impulsivity. Some hyperactive/impulsive symptoms may be present throughout childhood, although many individuals are diagnosed after the symptoms have been present for many years. In most cases, ADHD becomes apparent (and thus comes to medical attention) during the first few years of grade school. Some impairment from symptoms is present in at least 2 settings (e.g., home, school, or both). There is a clear trend toward symptomatic improvement in ADHD patients who have received pharmacological treatment. For example, in a study of methylphenidate treatment, children with ADHD who were treated with methylphenidate showed significant improvement in symptoms of inattention, hyperactivity, and impulsivity compared to placebo-controlled trials. In addition, methylphenidate has been shown to improve academic performance, reduce problems in the classroom, and improve quality of life for both children and their families. The long-term effects of methylphenidate treatment are not fully understood, and further research is needed to elucidate the potential risks and benefits of this medication.
Methylphenidate is the most extensively studied and frequently prescribed drug for the treatment of ADHD. However, few, if any, differences have been found between methylphenidate, dextroamphetamine, and pemoline (no longer commercially available in the US) or versus no medication or placebo in some evaluation including studies in children with ADHD, and the choice of stimulant therapy should be individualized. However, because the toxicities of stimulants have been associated with pemoline, some experts recommend its use only in patients who fail to respond to adequate trials of methylphenidate and an amphetamine. Methylphenidate is the most popular and efficacious drug in the treatment of ADHD and persistent target symptoms that are sufficiently severe to cause functional impairment at school; functional impairment usually also is evident at home and with peers. The risks of drug therapy must be weighed carefully with the risks of the untreated disorder, and the expected benefits of drug therapy must be weighed relative to other treatment options. Drug therapy should not be used as a substitute for appropriate educational curricula, student-teacher ratios, or other environmental accommodations. When severe impulsivity, noncompliance, or aggression is present, the need to initiate drug therapy may be more urgent.

Stimulants and dextroamphetamine (up to 16 months' duration) have shown unequivocal beneficial effects of the stimulants on the defining core symptoms of ADHD (attention and concentration, activity, distractibility, impulsivity, and associated aggressiveness) during continued therapy with the drugs. The response rate for any single stimulant drug in ADHD is about 70%, and at least 80% of children respond to a single stimulant. The majority of children experience little or no change in behavioral or academic symptoms if therapy is terminated. Children who fail to show positive therapeutic effects or who experience intolerable adverse effects with one stimulant should be tried on an alternative stimulant. Patients who do not respond to stimulants may also respond to clonidine and bupropion or other alternative therapy in the treatment of ADHD. Tricyclic antidepressants generally have been shown to be effective in the management of ADHD in children and adolescents, but are associated with a narrower margin of safety. In addition, although these agents have not been established, several researchers have reported that desipramine, which has been shown to be effective in the management of ADHD in children and adolescents, but is not approved for use in children less than 12 years of age.

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For the management of comorbid intermittent explosive disorder in children with ADHD, mood stabilizing agents (e.g., lithium or valproic acid) are recommended as adjuncts to stimulant therapy. Clonidine, an α2-adrenergic agonist, is not recommended in the management of comorbid aggressive symptoms as an adjunct to methylphenidate therapy; however, this is controversial and further study is needed to evaluate efficacy of such comorbid symptom and the potential risk of development of serious cardiovascular effects. Although carbamazepine has been widely used for the treatment of aggression in adults, its efficacy in children remains to be studied. In one controlled trial, the use of the drug failed to reduce aggression in children. Further studies are needed to evaluate the role of carbamazepine in the treatment of intermittent explosive disorder in children with ADHD. In addition, some experts no longer recommend use of typical antipsychotic (neuroleptic) agents because of the potential risk of withdrawal and neuroleptic dyskinesia. In contrast, use of risperidone (an atypical antipsychotic agent) may be considered in severely aggressive children with ADHD, in whom other treatments have failed.

Adolescents and Adults. Stimulants have been used effectively in the management of ADHD in adolescents and adults, but experience is far less extensive than in children and potential adverse effects in adults should be considered. Stimulants should be used cautiously in adults with comorbid substance abuse disorders.

Narcolepsy. Methylphenidate is used in the symptomatic treatment of narcolepsy. Methylphenidate has been used with equivocal results in the treatment of apathetic or withdrawn, somnolent behavior and mild depression, but the drug should not be used in the treatment of endogenous depression or opiate withdrawal states since anxiety may be aggravated.

Dosage and Administration

Administration Methylphenidate hydrochloride is administered orally. Methylphenidate is administered percutaneously by topical application of a transdermal system.

Oral Administration To avoid insomnia, the last daily dose of conventional (immediate-release) preparations should be given several hours before retiring.

Methylphenidate hydrochloride chewable tablets should be administered with a full glass (i.e., at least 240 mL [8 ounces]) of water or other fluid to avoid local irritation. (See Preparations Associated with Specific Immediate-Release Tablets under Cautions: Precautions and Contraindications.)

The extended-release tablets and extended-release trilayer core tablets of methylphenidate hydrochloride should be swallowed intact and should not be crushed or chewed. The extended-release capsules (Mexitidate® CD, Ritalin® LA) may be swallowed intact or the entire contents of a capsule(s) may be sprinkled onto a small amount (e.g., one tablespoonful) of applesauce immediately prior to administration. The manufacturer of Ritalin® LA states that the capsule contents should not be mixed with warm applesauce because the release properties of the formulation could be affected. The sprinkled/applesauce mixture should be taken immediately; the sprinkled/applesauce mixture must not be stored for use at a later time. One manufacturer suggests that the patient should drink fluids immediately after swallowing the intact capsule or sprinkled/applesauce mixture. Subdividing the contents of a capsule is not recommended, and crushing or chewing of the extended-release capsule or the capsule contents should be avoided.

Patients receiving methylphenidate hydrochloride extended-release trilayer core tablets (Concerta®) should be instructed not to become concerned if they notice a taste or a smell associated with the tablet. This is normal since the tablet containing the drug is designed to remain intact until it is swallowed. The system is constructed from a nonabsorbable shell during passage through the GI tract. The manufacturer states that it is possible that the extended-release trilayer core tablets may be visible on abdominal radiographs under certain circumstances, particularly when digital radiographic techniques are utilized.

Transdermal Administration Patients receiving transdermal methylphenidate should be carefully instructed in the proper use and disposal of the transdermal system.

The transdermal methylphenidate system should be applied once daily in the morning. The transdermal system should be removed 9 hours after application. The system should be applied immediately after opening the package and removing the protective liner; the system should not be used if the package seal is broken. The adhesive side of the transdermal system should be placed on a clean, dry area of the skin that is not oily, damaged, or irritated; approximately 1 inch from the incision site. The transdermal system should be reapplied to the same location or to a different location during each 28-day interval. Medication should be removed 9 hours after application. The system should be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure that there is good contact with the skin, particularly around the edges of the system. Application sites should be alternated daily (opposite arm) if possible.

Following proper application of the transdermal system, bathing, swimming, or showering has not been shown to affect adherence to the skin. If a system becomes dislodged during the intended period of use, it should be repositioned on the skin by the patient. If a system is removed prematurely, it should be folded so that the adhesive side adheres to itself and then be flushed down the toilet or disposed of in an appropriate lidded container. Any unused systems that are no longer needed should be removed from the skin. If a system is removed before the intended period of use, the drug will be removed without any risk to the patient. The patient should be instructed to replace the drug if the system is not in proper position on the skin. The patient should be instructed to keep the system in an upright position and to avoid bending, crumpling, or folding the system. If a system is left in place for more than 28 days, the patient should be instructed to remove it and replace it with a new system. If a system is removed prematurely, it should be folded so that the adhesive side adheres to itself, and then be flushed down the toilet or disposed of in an appropriate lidded container.

The manufacturer encourages parents to record on the administration chart included with each carton the time that the transdermal system was applied and the time that the system was removed. This information is needed to determine if the system was removed prematurely or if the patient is taking the drug as prescribed. If the information is not recorded, the drug may be needed for a longer period of time than expected. If the information is recorded, it may be possible to determine whether the drug is being taken as prescribed.

Dosage Methylphenidate hydrochloride must be carefully adjusted according to individual requirements and response. The extended-release dosage regimen should be initiated not later than 6 hours after the morning dose of the extended-release tablets. The extended-release tablets should be used and given at 8-hour intervals when the 8-hour dosage of the extended-release preparation corresponds to the titrated 8-hour dosage of the conventional tablets. Alternatively, dosage may be initiated with the methylphenidate hydrochloride extended-release trilayer core tablets and the extended-release tablets used for maintenance dosing. The extended-release tablets should be used and given at 8-hour intervals when the 8-hour dosage of the extended-release preparation corresponds to the titrated 8-hour dosage of the conventional tablets. Alternatively, dosage may be initiated with the methylphenidate hydrochloride extended-release trilayer core tablets and the extended-release tablets used for maintenance dosing.

After removal, used systems should be folded so that the adhesive side adheres to itself and then be flushed down the toilet or disposed of in an appropriate lidded container. Any unused systems that are no longer needed should be removed from the skin. If a system is removed prematurely, it should be folded so that the adhesive side adheres to itself, and then be flushed down the toilet or disposed of in an appropriate lidded container.

The manufacturer encourages parents to record on the administration chart included with each carton the time that the transdermal system was applied and the time that the system was removed. This information is needed to determine if the system was removed prematurely or if the patient is taking the drug as prescribed. If the information is not recorded, the drug may be needed for a longer period of time than expected. If the information is recorded, it may be possible to determine whether the drug is being taken as prescribed.
Intermediate-acting Oral Preparations. Methylphenidate hydrochloride extended-release tablets (Ritalin® ER, Methylin® ER, Ritalin® SR) may be used as an adjunct in the treatment of ADHD in children 6 years of age and older in patients whose ADHD symptoms are not controlled with methylphenidate extended-release tablets. The manufacturers suggest that extended-release methylphenidate hydrochloride tablets can be substituted for the conventional tablets at the nearest equivalent total daily dosage. For example, patients receiving 10 mg of conventional tablets in the morning and at noon can be switched to the extended-release form at an initial methylnidate dosage of 20 mg tablet administered once daily in the morning. In some patients, supplemental doses of a short-acting (conventional) preparation may be needed. The usual dosage of methylphenidate hydrochloride administered as an intermediate-acting oral preparation is 20–30 mg once daily or 30 mg in the morning and 20 mg in the afternoon.

Long-acting Oral Preparations. Methylphenidate hydrochloride extended-release capsules (Concerta® CD, Ritalin® LA) may also be used as an adjunct in the treatment of ADHD in children 6 years of age and older. The initial dosage of methylphenidate hydrochloride extended-release capsules is 20 mg once daily. The dosage may be increased by 10 mg at weekly intervals, until an optimum response is achieved or until a maximum dosage of 60 mg every morning is reached. Some clinicians state that patients currently receiving methylphenidate hydrochloride conventional tablets may be switched to Metadate® CD extended-release capsules. Patients being transferred from methylphenidate therapy using conventional tablets at a dosage of 10 mg twice daily can be switched to a dosage of 20 mg every morning as Metadate® CD extended-release capsules. Patients receiving methylphenidate hydrochloride therapy using conventional tablets at a dosage of 10 mg twice daily can be switched to a dosage of 30 mg every morning as Ritalin® LA extended-release capsules.

Patients receiving methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 10 mg twice daily can be switched to a dosage of 20 mg every morning as Metadate® CD extended-release capsules. Patients being transferred from methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 15 mg twice daily can be switched to a dosage of 30 mg every morning as Ritalin® LA extended-release capsules. Patients receiving methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 20 mg twice daily can be switched to a dosage of 40 mg every morning as Metadate® CD extended-release capsules. The manufacturer of Ritalin® LA extended-release capsules states that patients receiving conventional or extended-release methylphenidate hydrochloride tablets may be switched to Ritalin® LA extended-release capsules. Patients being transferred from conventional therapy using a conventional tablet at a dosage of 12 mg of methylphenidate hydrochloride extended-release core tablets may be switched to a dosage of 20 mg every morning as Ritalin® LA extended-release capsules. Patients receiving methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 15 mg twice daily can be switched to a dosage of 30 mg every morning as Ritalin® LA extended-release capsules. Patients receiving methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 20 mg twice daily can be switched to a dosage of 40 mg every morning as Ritalin® LA extended-release capsules. Patients receiving methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 30 mg twice daily can be switched to a dosage of 60 mg every morning as Ritalin® LA extended-release capsules. For other conventional or extended-release tablets regimens, the nearest daily dosage can be substituted based on clinical judgment. The manufacturer of extended-release methylphenidate hydrochloride trilayer core tablets states that patients receiving conventional methylphenidate hydrochloride tablets may be switched to Concerta® extended-release trilayer core tablets. Patients being transferred from methylphenidate hydrochloride conventional tablets at a dosage of 15 mg twice daily can be switched to a dosage of 15 mg twice daily or 30 mg once daily as the extended-release trilayer core tablets. Patients receiving methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 15 mg twice daily can be switched to a dosage of 30 mg every morning as the extended-release trilayer core tablets. The initial dosage of methylphenidate hydrochloride as extended-release trilayer core tablets in patients being switched from conventional methylphenidate tablets is 30 mg. In 35% of children with ADHD values between 27 mg and 34 mg every morning as extended-release capsules, and in 13% of children with ADHD receiving the drug as a transdermal system in clinical trials. Nervousness and insomnia usually can be controlled by reducing dosage and not administering the drug in the afternoon or evening. Headache has been reported in 9–14% of children and adolescents with ADHD receiving methylphenidate hydrochloride extended-release trilayer
Methylphenidate is a stimulant used to treat attention deficit hyperactivity disorder (ADHD). It is available in several formulations, including extended-release tablets in clinical trials. Nausea and vomiting were reported in 2% of children with ADHD receiving methylphenidate extended-release capsules in clinical trials. In 2 uncontrolled studies, the cumulative incidence of new-onset tics in children receiving methylphenidate hydrochloride extended-release tablets was reported to be 96% after 6 months of treatment (first study) and 15% after up to 24 months of treatment (second study). Tics were reported in 7% of children with ADHD receiving methylphenidate as a transdermal system in clinical trials.

Toxic psychosis and Tourette’s syndrome have been reported rarely in patients receiving methylphenidate. Neurologic malignant syndrome (NMS) also has been reported rarely in patients receiving methylphenidate; patients also were receiving other drugs that have been associated with NMS. An NMS-like syndrome developed in one 10-year-old boy who had been receiving methylphenidate for about 18 months; 45 minutes after ingesting the first dose of flunarizine, it is not known if such a reaction was associated with amphetamines or if it represented a drug interaction between methylphenidate and flunarizine or, alternatively, if the reaction was of unknown etiology.

Other adverse effects of methylphenidate include akathisia, dyskinesia, drowsiness, and aggressive behavior. Depression, anxiety, abnormal behavior, irritability, and suicidal behavior (including completed suicide) have been reported in patients receiving methylphenidate, but a causal relationship to the drug has not been definitively established.

GI and Growth Effects Abdominal pain and anorexia have been reported in 7% to 4%, respectively, of children and adolescents with ADHD receiving methylphenidate hydrochloride extended-release tablets in clinical trials and in 7% and 9%, respectively, of children with ADHD receiving methylphenidate extended-release capsules (Metadate CD) in clinical trials. Anorexia has also been reported in about 3% of children with ADHD receiving methylphenidate extended-release capsules. Results of one study suggest that protonated methylphenidate hydrochloride (40-80 mg daily) may cause suppression of normal weight gain in children. Results of an analysis of weight and height patterns in children 7 to 13 years of age suggested that treatment with methylphenidate for up to 3 years was associated with a temporary slowing in growth rate on average, height gain was suppressed by about 2 cm and weight gain was suppressed by about 1 kg over the first year. Without evidence of growth rebound during this period of development. Published data are inadequate to determine whether long-term use of amphetamines may cause similar suppression of growth; however, it is anticipated that amphetamines, like methylphenidate, also cause temporary growth suppression. Therefore, the manufacturers of stimulant preparations state that growth should be monitored during therapy with stimulants, and children who are not growing or gaining height or weight as expected may require temporary discontinuance of therapy. Although concerns about potential dose-related growth delays in children have been raised, a prospective follow-up study in girls with childhood-onset ADHD failed to show any significant impact on growth achieved in general. Studies of stimulants in children have found little or no decrease in expected height, with any decrease in growth in early treatment being compensated for later on. Although drug holidays during summer have been suggested to minimize weight loss and other potential adverse effects, these assumptions are based on a lack of data from controlled studies, and the evidence for the need for drug holidays is currently not known. (See Precautions Associated with Specific Methylphenidate Formulations under Cautions: Precautions and Contraindications.)

Hematologic Effects Thrombocytopenia and/or easy bruisability, epistaxis, and gingival bleeding have been reported in children receiving methylphenidate, but a causal relationship to the drug has not been definitively established.

Hematoxic effects such as hepatic and renal dysfunction have occurred in patients receiving methylphenidate. Although a definite causal relationship has not been established, hepatoxicity was associated with methylphenidate therapy in at least one patient.

Hepatic Effects Abnormal liver function, ranging from serum ammonia elevation (transaminases) elevations in liver function tests to moderate elevation of serum alkaline phosphatase, has been reported in patients receiving methylphenidate, although a definite causal relationship has not been established. Hepatotoxicity was associated with methylphenidate therapy in at least one patient.

Dermatologic and Sensitivity Reactions Hypersensitivity reactions including rash, urticaria, fever, anaphylaxis, exfoliative dermatitis, erythema multiforme with histopathologic findings of necrotizing venules, and thrombotic purpura may occur in patients receiving methylphenidate. Stevens-Johnson syndrome has been reported rarely. Fixed drug eruption has been reported in patients receiving methylphenidate, although a definite causal relationship has not been established. Erythema occurs in a majority of patients receiving methylphenidate as a transdermal system but generally is limited to the application sites. (See Cardiovascular Precautions under Cautions: Precautions and Contraindications.)

In a study evaluating the potential for methylphenidate transdermal system to cause contact sensitization, continuous exposure of the same skin site to transdermal methylphenidate for 3 weeks resulted in contact sensitization; contact sensitization was confirmed by rechallenge in some individuals. Contact sensitization has not been reported in patients who used the transdermal system as prescribed (i.e., alternating application sites on the hips). However, because sensitization was not specifically assessed in efficacy studies, the incidence of contact sensitization related to the transdermal system used in clinical trials is currently not known. (See Precautions Associated with Specific Methylphenidate Formulations under Cautions: Precautions and Contraindications.)

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Cardiovascular Effects Sudden death, stroke, myocardial infarction, angina, tachycardia, cardiac arrhythmia, palpitation, and increase or decrease in blood pressure and pulse rate may occur in patients receiving stimulants, including methylphenidate. (See Cardiovascular Precautions under Cautions: Precautions and Contraindications.) Isolated cases of cerebral aneurysis and/or cerebral hemorrhage have been reported in patients receiving methylphenidate. Cardiac arrhythmic, Raynaud’s phenomenon, peripheral coldness, and reversible ischemic neurologic deficit have been reported in patients receiving methylphenidate, although a definite causal relationship has not been established.

Other Adverse Effects Pulmonary granulomata, superficial abscesses, other foreign body reactions, and eosinophilia have been reported in patients receiving methylphenidate. Anaphylactic shock has been reported rarely in patients receiving methylphenidate tablets in water and the injected solution.

A few deaths have been reported rarely in patients receiving methylphenidate, but a causal relationship to the drug has not been definitely established. Death has been reported in patients receiving methylphenidate extended-release tablets in clinical trials.

Precautions and Contraindications Psychiatric Precautions Aggressive behavior and hostility frequently are observed in children and adolescents with ADHD and have been reported in patients receiving drug therapy for the disorder. Although a causal relationship to stimulants has not been established, patients beginning treatment for ADHD should be monitored for the occurrence of aggressive behavior. Psychotic or manic symptoms (e.g., hallucinations, delusional thinking, mania) have been reported in children and adolescents without prior history of psychotic illness or mania who received usual doses of stimulants. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% of patients receiving usual doses of stimulants (e.g., methylphenidate, amphetamine) compared with 0% of those receiving placebo. If psychotic or manic symptoms occur during stimulant therapy, a causal relationship to stimulants should be considered, and discontinuation of therapy should be considered. Precautions and Contraindications Associated with Specific Methylphenidate Formulations under Cautions: Precautions and Contraindications.

Stimulants should be used with caution in the management of ADHD in patients with comorbid bipolar disorder because of the potential for precipitation of mixed or manic episodes in such patients. Prior to initiating stimulant therapy, patients with ADHD and comorbid depressive symptoms should be carefully screened for the presence of bipolar disorder. Such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, or depression).

Stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder.

Each stimulant therapy education guide should be provided to the patient or caregiver, alerting them to the risks associated with stimulant therapy (e.g., adverse psychiatric effects, possible cardiovascular risks) and advising them of necessary precautions. (See Other Precautions and Contraindications under Cautions: Precautions and Contraindications.) Patients or their caregivers should be made aware of the importance of informing their physicians of preexisting illnesses or conditions, including suicidal ideation or behaviors or mental or psychiatric disorders. They also should be instructed to inform clinicians immediately if adverse psychiatric effects (e.g., hallucinations, delusional thinking, mania) occur during stimulant therapy.

Cardiovascular Precautions Stimulants, including methylphenidate, cause increased blood pressure and heart rate (i.e., about 2-3 mm Hg and heart rate, respectively, about 3-6 beats/minute); larger increases may occur in some patients. Although modest increases would not be expected to have short-term sequelae, all patients should be monitored for larger changes in blood pressure or heart rate. Caution should be exercised in persons with underlying medical conditions that might be affected by increases in blood pressure or heart rate (e.g., hypertension, heart failure, recent myocardial infarction, ventricular arrhythmia).

Although a causal relationship to stimulants has not been established, sudden unexplained death, stroke, and myocardial infarction have been reported in adults receiving usual doses of stimulants for the treatment of ADHD.
Sudden unexplained death also has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual doses of CNS stimulants. Results of one retrospective, case-control epidemiologic study showed that there may be an association between use of methylphenidate (e.g., enuresis, bedwetting) and sudden unexplained death in healthy children and adolescents. (See Cautions: Pediatric Precautions.) Given the study limitations, the US Food and Drug Administration (FDA) is unable to conclude that these data affect the overall risk and benefit profile of stimulant medications used to treat ADHD in children and adolescents. Abrupt stimulant discontinuation by parents of children or patients receiving these medications for ADHD before consulting with their clinician. Because of postmarketing reports and the results of this and other epidemiologic studies, FDA is conducting an ongoing review of the safety of methylphenidate and other stimulants in pediatric populations for use of these agents and sudden death in children. To determine whether there is a direct causal relationship between use of stimulants and serious adverse cardiovascular events, the Agency for Healthcare Research and Quality (AHRQ) and FDA announced in 2007 that they are collaborating on a large study to examine approximately 1,000,000 adults and children who received these drugs for management of ADHD during a 7-year period ending in 2005; data collection for the study is expected to be completed in 2009.

Children, adolescents, and adults who are being considered for stimulant therapy should undergo a thorough medical history review (including evaluation for a family history of sudden death or ventricular arrhythmia) and physical examination to detect the presence of cardiac disease, and should receive further cardiac evaluation (e.g., echocardiogram) if initial findings suggest such disease. Although some serious cardiac conditions are independently associated with an increased risk of sudden death, CNS stimulants generally should not be used in children, adolescents, or adults with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac conditions. Patients who develop abnormal chest pain, unexplained syncope, or other major cardiac suggestive of cardiac disease during stimulant therapy should undergo prompt cardiac evaluation.

Each time methylphenidate is dispensed, a medication guide should be provided to the patient or caregiver, alerting them to the risks associated with stimulant therapy (e.g., cardiovascular risks, adverse psychiatric effects) and advising them of necessary precautions. (See Other Precautions and Contraindications under Cautions: Precautions and Contraindications.) Patients or caregivers should be instructed to inform clinicians of preexisting illnesses or conditions, or cardiac disease. They also should be instructed to inform clinicians immediately if adverse cardiovascular effects (e.g., chest pain, shortness of breath, fainting) occur during stimulant therapy.

For further information on screening for cardiac conditions, selecting appropriate candidates for stimulant therapy, and monitoring for treatment-emergent cardiac conditions, see Cardiovascular Precautions and Contraindications, in the Amphetamines General Statement 28:29:04.

Precautions Associated with Specific Methylphenidate Formulations

Administration of methylphenidate hydrochloride chewable tablets, individually or in chewable tablets, may cause patients to swallow in blockage of the throat or esophagus and, possibly, choking. Therefore, chewable tablets should be taken with a full glass (i.e., at least 240 mL [8 ounces]) of water or other fluid and should not be administered in patients with difficulty swallowing. Patients should be advised to immediately seek medical attention if they experience vomiting, or difficulty in swallowing or breathing following administration of the chewable tablets.

Individuals with phenylketonuria (i.e., homozygous genetic deficiency of phenylalanine hydroxylase) and other individuals who must restrict their intake of phenylalanine should be informed that each 2.5-, 5-, or 10-mg chewable tablet contains sucrose (NutraSweet - ), which is metabolized in the GI tract to provide about 0.42, 0.84, or 1.68 mg, respectively, of phenylalanine following oral administration.

Methylphenidate hydrochloride extended-release tablets (Metadate CD) contain phenylalanine and should not be used in patients with hereditary phenylketonuria, intolerance, glucose-galactose malabsorption, or sucrose-isomaltose insufficiency.

Methylphenidate hydrochloride extended-release tablet core tablets generally should not be used in patients with previous severe GI narrowing since obstruction may occur.

Patients receiving the methylphenidate transdermal system should be advised to avoid exposing the application site to direct external heat sources (e.g., heating pads, electric blankets, heated water beds) while wearing the transdermal system. Releasing methylphenidate from the transdermal system is temperature dependent; release may increase more than twofold when the system is exposed to heat. (See Pharmacokinetics: Absorption.)

Use of the methylphenidate transdermal system may result in contact sensitization. Transdermal methylphenidate should be discontinued if contact sensitization occurs. The patient or caregiver should be informed by evidence of a more intense local reaction (e.g., edema, papules, vesicles) that does not improve substantially within 48 hours or that spreads beyond the application site. Diagnosis of allergic contact dermatitis should be confirmed by appropriate diagnostic testing. Patients sensitized from use of the methylphenidate transdermal system may develop systemic sensitization or other systemic reactions if methylphenidate-containing products are administered via other routes (e.g., orally). Manifestations of systemic sensitization may include a flare-up of previous dermatitis or of prior positive patch tests sites, or generalized skin eruptions in previously unaffected skin. Other systemic reactions may include angioedema, dyspnea, urticaria, and anaphylactic shock. Patients who develop contact sensitization to the methylphenidate transdermal system should be under close medical supervision if oral methylphenidate therapy is initiated.

Some patients sensitized to methylphenidate by exposure to the methylphenidate transdermal system may not be able to receive methylphenidate in any form.

Other Precautions and Contraindications

The manufacturer’s patient information (medication guide) should be provided to the patient or caregiver each time methylphenidate is dispensed, and the clinician should discuss and answer questions about its contents (e.g., benefits and risks of stimulant therapy). The patient or caregiver also should be instructed to read and understand the contents of the medication guide before initiating therapy and each time the prescription is refilled.

Patients or caregivers should be instructed to inform clinicians of preexisting illnesses or conditions (e.g., cardiac or cardiovascular disease/thyroid disease, seizures, history of substance abuse).

The manufacturer recommends libido tests, including periodic complete blood cell (with differential) and platelet counts, be performed periodically during prolonged methylphenidate hydrochloride therapy. However, anclotropine. Hyperactivity associated with methylphenidate therapy may occur as a direct causal relationship between use of methylphenidate and a causal relationship to the drug has not been conclusively established in these cases. Most clinicians consider routine hematologic monitoring (i.e., every 3 to 6 months) in the absence of clinical evidence (e.g., prolonged bleeding time, petechiae, or unusual bleeding or bruising) suggestive of possible hematologic toxicity, although some clinicians suggest annual hematologic monitoring in any patient receiving prolonged therapy with the drug. In addition, the American Academy of Pediatrics (AAP) states that routine hematologic, serologic, or ECG monitoring is not necessary during methylphenidate therapy.

- If paradoxical aggravation of symptoms occurs during methylphenidate therapy, dosage should be reduced or the drug discontinued.

Tolerance and psychological dependence with varying degrees of abnormal behavior have been reported in patients chronically taking large doses of methylphenidate. Frank psychotic episodes, including delusions, hallucinations, and, rarely, in those without a history of psychosis, have been reported in patients receiving methylphenidate. The drug should be administered with caution to patients with a history of chronic psychosis. The possibility of psychological or physical dependence should be considered, particularly when methylphenidate is administered to children, adolescents, or adults, or to patients with a history of drug abuse or addiction.

Abrupt withdrawal of methylphenidate following prolonged administration may unmask severe depression as well as the effects of chronic-overactivity; psychosis and suicidal ideation, dysphoric mood (i.e., depression, irritability, anxiety), agitation, delusions, or hallucinations, have been reported in patients receiving stimulants, including methylenidate.

Methylphenidate should be used with caution in patients with a history of seizures and/or EEG abnormalities. There is some clinical evidence that stimulants, including methylphenidate, may lower the seizure threshold in patients with or without a history of seizures; in those with prior EEG abnormalities, or with a history of seizures, and, very rarely, in those without a history of seizures and no prior evidence of EEG abnormalities. Although safe concomitant use of methylphenidate and anticonvulsants has not been established, studies of methylphenidate use have not shown an increase in seizure frequency or severity when the stimulant was used in patients receiving anticonvulsant therapy. If seizures occur in patients receiving methylphenidate, the drug should be discontinued.

Therapy with CNS stimulants may be associated with a least a temporary suppression of growth in children younger than 6 years of age, although this effect usually is not significant. Methylphenidate is contraindicated in patients with a history of marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Methylphenidate is also contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, and should be used with caution in patients with a history of or current porphyria. Methylphenidate is also contraindicated during or within 14 days of administration of monoamine oxidase inhibitors (MAOIs) inhibitors since hypertensive crisis can result. (See Drug Interactions.)

Pediatric Precautions

- Although safety and efficacy of methylphenidate in children younger than 6 years of age have not been established, the drug has been used in several controlled clinical studies in preschool-aged children up to 6 years of age. Some studies reported higher rates of adverse effects, particularly with higher dosages, than had previously been reported in children 6 years of age and older and the adverse effects reported in preschool-aged children may be different from those reported in older children with

Exhibit D.5, page 6
ADHD. Some of the adverse behavioral effects reported in clinical studies in preschool-aged children receiving methylphenidate also were reported in those receiving placebo; some of these behaviors may actually improve in preschool-aged children receiving methylphenidate therapy. Other issues involved with the use of stimulants in children younger than 6 years of age have been established dosage recommendations for this population. Additional study and experience are required to elucidate further the safety and efficacy of the drug in this age group.

Long-term administration of CNS stimulants has been associated with at least temporary suppression of normal weight and/or height patterns in children; patients requiring long-term therapy with methylphenidate should be carefully monitored and the drug should be discontinued temporarily in children in whom suppression of normal growth or weight gain is observed. However, studies that assess the growth of stimulants in children generally have found little or no decrease in expected height, with any decreases in growth rate in treatment being compensated for later on. (See Cautions: GI and Growth Effects.)

Sudden death has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving stimulant dosages of CNS stimulants. Results of one retrospective, case-control epidemiologic study suggested a possible association between use of stimulant medications and sudden unexpected death in healthy children and adolescents. (See Cardiovascular Precautions under Cautions: Precautions and Contraindications.)

Pregnancy and Lactation Although there are no adequate and controlled studies to date in humans, methylphenidate hydrochloride has been shown to have teratogenic effects in rabbits when given at doses 100 and 40 times the recommended human dosage on a mg/kg or mg/m² basis, respectively. Methylphenidate hydrochloride should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

It is not known whether methylphenidate is distributed into human milk. Because many drugs are distributed into human milk, caution should be exercised if methylphenidate is administered to a nursing woman.

Drug Interactions

• Antidepressants Because monoamine oxidase (MAO) inhibitors potentiate the pressor effects of sympathomimetic drugs, methylphenidate is contraindicated in patients currently receiving or having recently received (i.e., within 2 weeks) MAO inhibitor therapy. The metabolism of tricyclic antidepressants (e.g., imipramine, clomipramine, desipramine) has been reported to be inhibited when these drugs are used in patients receiving methylphenidate. Some manufacturers state that the metabolism of selective serotonin-reuptake inhibitors (SSRIs) may be inhibited when methylphenidate is used concomitantly. In adults, doses of tricyclic antidepressants and SSRIs may be required in patients receiving concomitant methylphenidate therapy.

• Cardiovascular Agents Methylphenidate should be used with caution in patients receiving pressor agents. Methylphenidate may antagonize the effects of antihypertensive agents (e.g., guanethidine [no longer commercially available in the US] or bretylium). Rare cases of serious adverse cardiovascular effects, including death, have occurred in patients receiving methylphenidate and clonidine concomitantly, although due to the presence of possibly confounding risk factors and lack of systematic evaluation, causality has not been established.

Other Drugs The metabolism of eumamm antisquidogals and anti-convulsants (e.g., phenobarbital, phenytoin, primidone) has been reported to be inhibited when these drugs are administered in patients receiving methylphenidate. Although additional studies did not confirm the reported inhibition of metabolism of anticonvulsants and eumamm antisquidogals, the possibility that methylphenidate may raise the serum concentrations of some of these drugs to toxic concentrations necessitating dose adjustments could be important. Additionally, metabolism of phenytoin and phenobarbital (no longer commercially available in the US), has been reported to be inhibited when administered in patients receiving methylphenidate hydrochloride conventional or extended-release tablets. Dosage reduction of eumamm antisquidogals, anticonvulsants, or phenytoin may be required in patients receiving concomitant methylphenidate therapy. It may be necessary to monitor plasma drug concentrations (or, in the case of eumamm antisquidogals, phenothrin tension [PT]) when methylphenidate is initiated or discontinued. It may be necessary to evaluate the effects of changes in gastric pH on the absorption of methylphenidate hydrochloride administered as extended-release capsules (Ritalin LA) if methylphenidate is administered. In the event of overdose involving methylphenidate, all therapeutic systems of the drug should be removed immediately and the skin cleansed of any remaining adhesive; the potential for continued absorption of residual drug in the skin following system removal should be considered. If signs and symptoms of acute toxicity are not too severe and the patient is conscious, generally following ingestion of oral dosage forms by induction of emesis or gastric lavage. In patients with severe intoxication, administration of a carefully titrated dose of a short-acting barbiturate may be required before beginning gastric lavage. External cooling procedures may be required if the patient is in a state of hyperthermia. Effectiveness of peritoneal dialysis or extracorporeal hemodialysis for the treatment of methylphenidate overdose has not been established.

Pharmacology

The pharmacologic actions of methylphenidate are qualitatively similar to those of the amphetamines and include CNS and voluntary skeletal muscle stimulation and weak sympathomimetic activity. The mechanism of action involved in the central effect of methylphenidate has not been determined. The main sites of CNS action appear to be the cerebral cortex and subcortical structures including the diencephalon. Amphetamine-like effects in monkeys include increased motor activity, mental alertness, diminished sense of fatigue, brighter spirits, and mild euphoria. Methylphenidate apparently produces an anorexigenic effect. In usual therapeutic oral dosage, methylphenidate exhibits only moderate effects on the peripheral circulatory system.

Pharmacokinetics

Absorption Methylphenidate hydrochloride appears to be well absorbed (from the GI tract; however, oral bioavailability of the drug is low (about 30%; range: 10-52%), whichsuggests substantial first-pass metabolism. Following oral administration of methylphenidate conventional or extended-release tablets, oral solution, or chewable tablets, peak plasma concentrations were attained at approximately 1-2 hours. Methylphenidate hydrochloride oral solution and chewable tablets are biotransformed to methylphenidate hydrochloride conventional tablets.

Methylphenidate conventional and extended-release tablets are absorbed more slowly but to the same extent as the conventional tablets. Following oral administration of methylphenidate hydrochloride 20 mg or 40 mg as extended-release capsules (Methyl­tilin ER, Ritalin SR) in children, peak plasma concentrations were attained at 4.7 hours. After oral administration of methylphenidate hydrochloride 20 mg or 40 mg as extended-release capsules (Methyl­tilin CD) in children, peak plasma concentrations were attained at 1.5 hours and again at 4.5 hours after a dose. In children, the mean peak plasma concentration and mean area under the plasma concentration-time curve (using linear trapezoidal rule) were slightly lower following administration of 20 mg of the drug once daily as Methyl­tilin CD extended-release capsules than following administration of 10 mg twice daily as conventional tablets. In children and adults, the relative bioavailability of Rit­alin - LA extended-release capsules (Methyl­tilin ER, Ritalin SR) administered three times daily is comparable to that of the conventional tablets administered twice daily 4 hours apart. The initial rate of absorption of methylphenidate hydrochloride and the time to first peak plasma concentration were similar following administration of 40 mg of the drug once daily as Ritalin LA extended-release capsules or 20 mg twice daily (given 8 hours apart) as conventional tablets, but greater interindividual variability and a smaller difference between peak and trough plasma concentrations (resulting from a lower second peak concentration and a higher minimum concentration between the 2 peak concentrations) were observed following extended-release tablets. Relative bioavailability of the extended-release trilayer core tablets of methylphenidate hydrochloride (Concerta) administered once daily is comparable to that of the conventional tablets administered 3 times daily. Following oral administration of the extended-release trilayer core tablets of methylphenidate hydrochloride in healthy adults, serum peak plasma concentrations increased from 24 mg/mL 2-4 hours after oral administration of 20 mg of methylphenidate hydrochloride extended-release tablets (Concerta) or extended-release capsules (Methyl­tilin CD, Ritalin LA) to approximately 70 mg/mL 4-6 hours after oral administration of 80 mg of ritaline extended-release tablets (Concerta).

Following application of a single transdermal system (Daytrana), peak plasma methylphenidate concentrations are attained within 7.5-10 hours. Application of the transdermal system to abdominal skin is associated with a shorter time to peak plasma concentration (4 hours) and a threefold increase in peak plasma concentration and AUC compared with application to intact skin. When heat is applied to the transdermal system after application, time to peak plasma concentration is less than one hour and peak plasma concentrations and AUC are 2.5-5-fold higher, respectively, than those observed following application without heat. Application sites other than the hip can have different absorption characteristics and have not been adequately studied. Some data suggest that transdermal absorption of methylphenidate may be increased by changing the administration site.

Effects persist for 3-6 hours after oral administration of conventional tablets, about 3-8 hours after oral administration of certain extended-release tablets (e.g., Methyl­tilin ER, Ritalin SR), and about 8-12 hours after oral administration of extended-release trilayer core tablets (Concerta) or extended-release capsules (e.g., Methyl­tilin CD, Ritalin LA)
Because of substantially greater first-pass metabolism following oral compared to transdermal administration, a lower transdermal dose of methylphenidate may result in greater systemic exposure to d-methylphenidate (the more pharmacologically active isomer). The commercially available transdermal system of methylphenidate consists of a laminate film backing layer, an adhesive layer containing the drug, and a protective liner attached to the adhesive surface. The methylphenidate dosage delivered is dependent on the size of the transdermal system and the length of time the system is worn.

**Precautions**

Methylphenidate hydrochloride is subject to control under the Federal Controlled Substances Act of 1970 as a schedule II (C-II) drug.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

**Chemistry and Stability**

- **Chemistry** Methylphenidate hydrochloride is a piperidine-derivative stimulant. The drug occurs as a fine, white, odorless, crystalline powder and is freely soluble in water and soluble in alcohol. Methylphenidate hydrochloride is commercially available as conventional tablets, chewable tablets, and an oral solution (Ritalin L A, Metadate CD, Ritalin LA) and methylphenidate transdermal systems should be stored at a controlled room temperature of 25°C, but may be exposed to temperatures ranging from 15-30°C. Methylphenidate hydrochloride oral solution and chewable tablets should be stored at 20-25°C.

**Methylphenidate**

<table>
<thead>
<tr>
<th>Topical System</th>
<th>Transdermal</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytrane (C-II)</td>
<td>10 mg/0 hours (27.5 mg/12.5 cm²)</td>
<td>Daytrane (C-II)</td>
</tr>
<tr>
<td>Daytrane (C-II)</td>
<td>15 mg/4 hours (41.3 mg/18.75 cm²)</td>
<td>Daytrane (C-II)</td>
</tr>
<tr>
<td>Daytrane (C-II)</td>
<td>20 mg/8 hours (55 mg/25 cm²)</td>
<td>Daytrane (C-II)</td>
</tr>
<tr>
<td>Daytrane (C-II)</td>
<td>30 mg/6 hours (82.5 mg/35.7 cm²)</td>
<td>Daytrane (C-II)</td>
</tr>
</tbody>
</table>

**Methylphenidate Hydrochloride**

<table>
<thead>
<tr>
<th>Oral Capsules, (containing beads)</th>
<th>Tablets (extended-release)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg (beads, extended-release 7 mg with 3 mg immediate-release)</td>
<td>Metadate CD (C-II), UCB</td>
</tr>
<tr>
<td>10 mg (beads, extended-release 5 mg with 5 mg immediate-release)</td>
<td>Ritalin LA (C-II), Novartis</td>
</tr>
<tr>
<td>20 mg (beads, extended-release 10 mg with 10 mg immediate-release)</td>
<td>Metadate CD (C-II), UCB</td>
</tr>
<tr>
<td>30 mg (beads, extended-release 15 mg with 15 mg immediate-release)</td>
<td>Metadate CD (C-II), UCB</td>
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<tr>
<td>40 mg (beads, extended-release 20 mg with 20 mg immediate-release)</td>
<td>Ritalin LA (C-II), Novartis</td>
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<tr>
<td>50 mg (beads, extended-release 25 mg with 25 mg immediate-release)</td>
<td>Metadate CD (C-II), UCB</td>
</tr>
<tr>
<td>60 mg (beads, extended-release 30 mg with 30 mg immediate-release)</td>
<td>Metadate CD (C-II), UCB</td>
</tr>
</tbody>
</table>

**Solution**

- **Methylphenidate Oral Solution (C-II)**, Sciele
- **Methylphenidate Oral Solution (C-II)**, Sciele

**Tablet**

- **Methylphenidate Hydrochloride Tablets (C-II)**, Novartis
- **Ritalin Hydrochloride (C-II)**, Novartis
- **Methylphenidate Hydrochloride Tablets (C-II)**, Novartis
- **Ritalin Hydrochloride (C-II)**, Novartis
- **Methylphenidate Hydrochloride Tablets (C-II)**, Novartis
- **Ritalin Hydrochloride (C-II)**, Novartis
Modafinil is a CNS stimulant that is structurally and pharmacologically distinct from other currently available CNS stimulants.

**Uses**

Modafinil is used to improve wakefulness in adults with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD). Careful attention to the diagnosis and treatment of the underlying sleep disorder is essential whenever modafinil is used in patients with these conditions. (See Diagnosis of Sleep Disorders under Warnings/Precautions: General Precautions, in Cautions.)

**Narcolepsy**

Modafinil is used in the symptomatic treatment of narcolepsy to improve wakefulness in adults with excessive daytime sleepiness (EDS). Narcolepsy is a CNS disorder characterized by somnolence, often accompanied by sudden attacks of sleepiness (cataplexy) while awake and during sleep, and occasionally by hypnagogic hallucinations and/or sleep paralysis before falling asleep or awakening. The disorder involves dysregulation of wakefulness and sleep.

Efficacy of modafinil has been established in the US in 2 double-blind, multicenter placebo-controlled clinical trials of 6 weeks' duration. In these and other clinical studies, modafinil 200 or 400 mg daily increased daytime wakefulness and alertness and decreased the number of daytime sleep episodes as determined by several objective (e.g., the Multiple Sleep Latency Test [MSLT], the Maintenance of Wakefulness Test [MWT], the Shear Clear Performance Test [SCT] in the morning and subjective, e.g., the Epworth Sleepiness Scale [ESS]) measures of sleepiness. Patients showed an enhanced ability to remain awake with both dosages relative to placebo at 3, 6, and 9 weeks, and at study end point (last post-baseline assessment while the patient was in the study) and also greater global improvement in the patient's overall sleepiness status (measured by the Clinical Global Impression—Change [CGI-C]). However, despite the clinical improvements, mean objective and subjective measures of sleepiness did not completely normalize with modafinil therapy, with a degree of clinically important physiologic sleepiness persisting despite therapy. The percentage of patients exhibiting any degree of increase in the objective measures of sleepiness was 59% in the CGI-C arm on week 2, and 40% in the ESS arm on week 2 of the double-blind placebo-controlled trials. The ESS was also well tolerated for up to 40 weeks of therapy, with 11% of patients discontinuing modafinil because of adverse effects and 14% because of inadequate therapeutic effect. Although most patients enrolled in the 2 clinical trials exhibited efficacy in the US had histories of cataplexy, those requiring anti-cataplectic therapy generally were excluded from enrollment. Therefore, current efficacy of modafinil in cataplexy is limited primarily to its effects on excessive daytime sleepiness. In one study in a limited number of patients, cataplexy was not affected by modafinil therapy.

Modafinil did not affect the initiation, maintenance, quality, or quantity of nighttime sleep and did not affect the ability to undergo sleep (SWS) during the daytime. Like other CNS stimulants modafinil can alter mood, perception, thinking, and feelings and can cause psychomotor and euphoric effects. However, in clinical trials, there was no clinically important association between modafinil and the incidence of agitation in patients. In animals, modafinil is retnotized to all major central nervous system (CNS) structures, with the exception of dopamine-containing neurons. Animal studies have demonstrated that modafinil is related to the CNS and peripheral anticholinergic, beta-adrenergic, antihistaminergic, and antiserotoninergic activity and can cause adverse effects associated with cholinergic, adrenergic, histaminergic, and serotoninergic activity in animals.

In the first multicenter, placebo-controlled study, which was of 12 weeks' duration, patients were randomized to receive modafinil 200 mg daily, modafinil 400 mg daily, or placebo. The majority of patients (80%) in this study were full compliers with CPAP (defined as CPAP use for more than 4 hours per night on more than 70% of nights). The drug was partially effective in the remaining patients. Efficacy of modafinil was principally evaluated by measurement of sleep latency as assessed by the Maintenance of Wakefulness Test (MWT) and in the patient's overall disease status as assessed by the Clinical Global Impression—Change (CGI-C) scale at the final visit. The modafinil-treated patients demonstrated a significant improvement in their ability to remain awake as measured by the MWT at the study end point and in their clinical condition as measured by the CGI-C compared with those receiving placebo. The 200- and 400-mg daily doses produced similar clinical efficacy in this study.

In the second multicenter, placebo-controlled study, which was of 4 weeks' duration, patients were randomized to receive either modafinil 400 mg daily or placebo. Documentation of regular CPAP use (for at least 4 hours each night on 7 of every 9 nights) was required for all patients. Efficacy in reducing daytime sleepiness was measured primarily by the change in the patient's ESS on the CGI-C scale at week 4 or the final visit. Patients who received modafinil demonstrated a significant reduction in their ESS score from baseline (mean score reduced by 1.6) compared with patients receiving placebo (mean scores reduced by 2). In addition, patients who received modafinil had significantly lower ESS scores than those receiving placebo (ESS score less than 10 was significantly higher for the modafinil group than for those receiving placebo [51% and 27%, respectively]). Nighttime sleep as measured by polysomnography was not affected by modafinil administration in these 2 studies.

The manufacturer states that the long-term efficacy (e.g., longer than 12 weeks) of modafinil in OSAHS has not been systematically evaluated in placebo-controlled studies to date. However, a 12-month, noncomparative extension phase of the 12-week, placebo-controlled trial in which patients received modafinil 200, 300, or 400 mg daily demonstrated substantial reductions in ESS scores. In this study, there were no statically significant differences in sleep parameters based on the CGI-C and ESS scores compared with baseline. At 1 year, patients were monitored without changes in CPAP therapy.

When modafinil is used for extended periods, the need for continued therapy should be reassessed periodically.

**Shift Work Sleep Disorder**

Modafinil is used in the symptomatic treatment of SWSD to improve wakefulness in adults with excessive sleepiness. Criteria of the International Classification of Sleep Disorders (ICSD-10) for SWSD include an inability to sleep at night and the need for extended daytime sleep to maintain performance during the work period.
Use of desvenlafaxine with aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided or used with caution due to an increased risk of bleeding.

Advice to Patients

Risk of suicidality: If a patient experiences any of the following symptoms, they should be advised to discontinue desvenlafaxine and seek medical advice immediately:
- thoughts of harming or killing oneself, or suicide
- any other abnormal or worsening conditions

Importance of informing patients that they may notice an inert matrix tablet passing in the stool or via colostomy, and that the active medication has already been absorbed by the time the patient sees the inert matrix tablet.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Desvenlafaxine Succinate

Uses

- Major Depressive Disorder: Duloxetine hydrochloride is used for the acute and maintenance treatment of major depressive disorder in adults. Duloxetine hydrochloride is a serotonin-norepinephrine reuptake inhibitor (SNRI).

- Generalized Anxiety Disorder: Duloxetine hydrochloride is used for the acute management of generalized anxiety disorder in adults. Duloxetine hydrochloride is also used for the management of neuropathic pain associated with diabetic peripheral neuropathy.

- Neuropathic Pain: Duloxetine hydrochloride is used for the management of neuropathic pain associated with diabetic peripheral neuropathy.

Importance of advising patients to stop taking desvenlafaxine without first talking with their clinician. Importance of patients being aware that discontinuation effects may occur when stopping the drug.

Importance of informing patients to swallow desvenlafaxine extended-release tablets whole, and not to crush, cut, chew, or dissolve the tablets.

Importance of informing patients that duloxetine tablets contain an inert matrix tablet passing in the stool or via colostomy, and that the active medication has already been absorbed by the time the patient sees the inert matrix tablet.

Importance of informing patients of other important precautionary information. (See Cautions.)
Duloxetine

Efficacy of duloxetine for the treatment of chronic pain syndromes: A systematic review and meta-analysis.

**Major Depressive Disorder**
For the treatment of major depressive disorder, the recommended initial adult dosage of duloxetine is 60 mg daily (given as 20 mg twice daily) to 120 mg daily (given as 60 mg once daily). In some patients, it may be desirable to initiate therapy with a dosage of 30 mg once daily for 1 week, followed by an increase of 10 mg for each week of therapy (i.e., reaching a dosage of 60 mg once daily after 3 weeks). The manufacturer recommends that if adverse effects are bothersome during the first 4 weeks of therapy, the dosage may be reduced to 60 mg once daily. Duloxetine dosages exceeding 60 mg daily do not appear to provide substantially greater therapeutic benefit and are less well tolerated. For patients for whom tolerability is a concern, a lower initial dosage may be considered. Duloxetine's antidepressant efficacy is highly variable and management of pain is empirical. Efficacy of the drug must be assessed individually. The manufacturer states that the efficacy of duloxetine for long-term use (i.e., exceeding 12 weeks) has not been established by controlled studies and that the usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

**Neuropathic Pain**
For the management of neuropathic pain associated with diabetic peripheral neuropathy, the recommended initial adult dosage of duloxetine is 60 mg once daily. Duloxetine dosages exceeding 60 mg daily do not appear to provide substantially greater therapeutic benefit and clearly are less well tolerated. For patients for whom tolerability is a concern, a lower initial dosage may be considered. Duloxetine's antidepressant efficacy is highly variable and management of pain is empirical. Efficacy of the drug must be assessed individually. The manufacturer states that the efficacy of duloxetine for long-term use (i.e., exceeding 12 weeks) has not been established by controlled studies and that the usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

**Fibromyalgia**
For the management of fibromyalgia, the recommended initial adult dosage of duloxetine is 60 mg once daily. The manufacturer states that treatment should be initiated at 30 mg once daily for one week to allow patients to adjust to the drug before increasing the dosage to 60 mg once daily. Some patients may require the initial dosage of 30 mg once daily. Duloxetine dosages exceeding 60 mg daily appear to provide substantially greater therapeutic benefit, even in patients not responding to a dosage of 60 mg daily, and are associated with a higher incidence of adverse effects.

**Bipolar Disorder**
Duloxetine is used for the management of manic or mixed episodes associated with bipolar disorder as add-on therapy in patients receiving stable doses of mood-stabilizing medications. The recommended initial adult dosage of duloxetine is 60 mg once daily, with a maximum dosage of 80 mg daily. Duloxetine dosage may be increased in 20-mg increments every 1-2 weeks to a maximum of 80 mg daily. Duloxetine dosages exceeding 80 mg daily do not appear to provide substantially greater therapeutic benefit and are less well tolerated. For patients for whom tolerability is a concern, a lower initial dosage may be considered. Duloxetine's antidepressant efficacy is highly variable and management of pain is empirical. Efficacy of the drug must be assessed individually. The manufacturer states that the efficacy of duloxetine for long-term use (i.e., exceeding 12 weeks) has not been established by controlled studies and that the usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

**Generalized Anxiety Disorder**
For the treatment of generalized anxiety disorder, the recommended initial adult dosage of duloxetine is 60 mg once daily. The dosage may be increased by 10 mg for each week of therapy (i.e., reaching a dosage of 60 mg once daily after 3 weeks). The manufacturer recommends that the decision to continue therapy with the drug be based on individual patient response.
Duloxetine - SELECTIVE SEROTONIN- AND NORADRENERGIC-REUPTAKE INHIBITORS

- Contraindications
  - Concurrent or recent (i.e., within 2 weeks) therapy with a monoamine oxidase (MAO) inhibitor. (See Drug Interactions: Monoamine Oxidase Inhibitors.)
  - Uncontrolled angle-closure glaucoma.

- Warnings/Precautions
  - Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric patients (see Pediatric Use under Cautions: Specific Populations, in Cautions.)

- Cautions
  - Concomitant Illnesses. Experience with duloxetine in patients with concomitant illness has not been established. (See Concomitant Illnesses under Warnings/Precautions: Other Warnings and Precautions, in Cautions and also see Drug Interactions: Monoamine Oxidase Inhibitors.)

- Other Warnings and Precautions

  - Hepatic Effects. Hepatic failure, sometimes fatal, has occurred in duloxetine-treated patients. These failures have been associated with hepatitis, abdominal pain, jaundice, and/or ascites. The mortality rate in these circumstances was 100%. The manufacturer recommends that patients with a history of liver disease or with elevated hepatic enzyme levels be monitored closely during treatment and that careful consideration be given to continuing therapy in patients with a history of liver disease or with elevated hepatic enzyme levels. (See Hepatic Failure under Warnings/Precautions: Other Warnings and Precautions, in Cautions and also see Drug Interactions: Monoamine Oxidase Inhibitors.)

  - Cases of cholestatic jaundice with minimal elevation of serum transaminase concentrations have been reported in duloxetine-treated patients. Some of these failures were associated with abdominal pain, jaundice, and/or ascites. The mortality rate in these circumstances was 100%. The manufacturer recommends that patients with a history of liver disease or with elevated hepatic enzyme levels be monitored closely during treatment and that careful consideration be given to continuing therapy in patients with a history of liver disease or with elevated hepatic enzyme levels. (See Hepatic Failure under Warnings/Precautions: Other Warnings and Precautions, in Cautions and also see Drug Interactions: Monoamine Oxidase Inhibitors.)

  - Duloxetine has been shown to increase the risk of serum transaminase elevations in clinical trials; such elevations resulted in discontinuation of the drug in 0.3% of patients. The median time to detection of the transaminase elevation was about 2 months. In placebo-controlled trials, elevations in serum ALT concentrations greater than 3 times the upper limit of normal occurred in 0.3% of patients on duloxetine, compared with 0.2% of patients receiving placebo. There was evidence of a dose-response relationship for ALT (SGPT) and AST (SGOT) elevations of more than 3 times the upper limit of normal and more than 5 times the upper limit of normal during treatment with duloxetine. (See Hepatic Failure under Warnings/Precautions: Other Warnings and Precautions, in Cautions and also see Drug Interactions: Monoamine Oxidase Inhibitors.)

  - Because of the possibility that duloxetine and alcohol may interact to cause hepatic injury or that duloxetine may aggravate preexisting hepatic disease, duloxetine should not be coadministered with alcohol. Patients and/or caregivers should be advised to avoid concurrent use of alcohol or other potentially hepatotoxic substances and to report any symptoms of liver injury immediately. (See Hepatic Failure under Warnings/Precautions: Other Warnings and Precautions, in Cautions and also see Drug Interactions: Monoamine Oxidase Inhibitors.)

  - Orthostatic Hypotension and Syncope. Orthostatic hypotension and syncope have been reported with therapeutic dosages; although these effects tend to occur within the first week of therapy, they may occur at any time during therapy; particularly following increases in dosage. Risk of decreased blood pressure may be greater in patients concomitantly receiving other drugs that produce orthostatic hypotension (such as antihypertensive agents); in patients receiving potent inhibitors of the cytochrome P-450 (CYP) 1A2 isoenzyme (see Drug Interactions: Drugs Affecting Hepatic Microsomal Enzymes); or in those receiving duloxetine exceeding 60 mg/d. Discontinuation of the drug should be considered in patients experiencing symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

  - Serotonin Syndrome. Potentially life-threatening serotonin syndrome can occur with other serotonergic drugs, particularly with concurrent administration of other serotonergic drugs (e.g., serotonin [5-hydroxytryptamine; 5-HT] type 1 receptor agonists ["triptans"] or drugs that impair serotonin metabolism [e.g., monoamine oxidase [MAO] inhibitors]). Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hypertonia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea).

  - To monitor patients on a daily basis for the emergence of agitation, irritability, and the emergence of suicidal ideation and behavior (suicidality), or unusual changes in behavior, particularly during initiation of therapy, when dosage is increased, or when another serotoninergic agent is initiated.

  - Concomitant use of duloxetine and serotonin precursors (e.g., tryptophan) is not recommended.

  - Abnormal Bleeding. SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concurrent administration of aspirin, nonsteroidal anti-inflammatory agents, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiologic studies have demonstrated an association between the use of drugs that interfere with serotonin reuptake and the occurrence of bleeding events related to SSRIs and SNRI use. These events have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. The manufacturer recommends that patients be advised of the risk of bleeding associated with the concomitant use of duloxetine and other strong inhibitors of serotonin reuptake. (See Drug Interactions: Drugs Affecting Hemostasis.)

  - Withdrawing Effects. Because withdrawal effects (e.g., dysphoric mood, irritability, agitation, nausea/vomiting, dizziness, sexual dysfunction, insomnia, nightmares, headache, dizziness, sweating, paresthesias, pruritus) may occur when discontinuing treatment with duloxetine, patients should be advised to taper their dose gradually. The manufacturer recommends that patients be advised of the risk of withdrawal effects when discontinuing treatment with duloxetine. (See Drug Interactions: Monoamine Oxidase Inhibitors.)

  - Activation of Mania/Hypomania. Activation of mania and hypomania has occurred in patients with major depressive disorder receiving duloxetine. Use with caution in patients with a history of mania.

  - Seizures. The risk of seizures associated with duloxetine use has not been systematically evaluated, but seizures have been reported in patients receiving duloxetine. Use with caution in patients with a history of seizure disorder.

  - Blood Pressure. May increase blood pressure. Monitor blood pressure prior to and during duloxetine therapy.

  - Clinically Important Drug Interactions. Because both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism, the potential exists for CYP1A2 and CYP2D6 inhibitors and/or inducers to affect the metabolism of duloxetine. (See Drug Interactions: Monoamine Oxidase Inhibitors.)

  - Concomitant therapy with MAO inhibitors used for treatment of depression is contraindicated. (See Drug Interactions: Monoamine Oxidase Inhibitors.)

  - Concurrent treatment with MAO inhibitors used for treatment of depression can lead to the accumulation of noradrenaline in the brain, and can increase the risk of hypertensive crisis. (See Drug Interactions: Monoamine Oxidase Inhibitors.)

  - Hypertension/Syndrome of Inappropriate Antidiuretic Hormone Secretion. Treatment with SSRIs and SNRIs including duloxetine may result in hypotension. In many cases, hypotension appears to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium concentrations lower than 110 mmol/L have been reported and hypertension appeared reversible when duloxetine was discontinued. Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be more susceptible to volume changes related to SIADH. Cases of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls; more severe and/or acute cases have been associated with hallucinations, seizures, syncope, coma, respiratory arrest, and death. (See Drug Interactions: Monoamine Oxidase Inhibitors.)

  - Consult Contraindicated. Experience with duloxetine in patients with concomitant diseases is limited. (See Hepatic Impairment and see Renal Impairment under Warnings/Precautions: Specific Populations, in Cautions.)
Exhibit D.6, page 4
Duloxetine Hydrochloride

- **SELECTIVE SEROTONIN- AND NORADRENALINE-REUPTAKE INHIBITORS**

- **CNS-active Drugs**: Potential pharmacologic interaction when given with or substituted for other centrally acting drugs, including those with a similar mechanism of action; use with caution.

- **5-HT, Receptor Agonists ("Triptans")**: Pharmacologic interaction (potentially life-threatening serotonin syndrome) if used concurrently with 5-HT, receptor agonists (e.g., almotriptan, eltrotrip坦, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan). If concurrent use is elected, the patient should be observed carefully, particularly during treatment initiation, when dosage is increased, or when another serotonin agonist is initiated. (See Serotonin Syndrome under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

- **Monoamine Oxidase (MAO) Inhibitors**: Pharmacologic interaction (potentially life-threatening serotonin syndrome) if used concurrently. Concomitant administration is contraindicated. The manufacturer recommends that at least 2 weeks elapse between discontinuance of an MAO inhibitor and initiation of duloxetine and that at least 5 days elapse between discontinuance of duloxetine therapy and initiation of MAO inhibitor therapy. (See Serotonin Syndrome under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

- **Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Noradrenaline-reuptake Inhibitors**: Potential pharmacologic interaction (potentially life-threatening serotonin syndrome); concurrent administration not recommended. (See Serotonin Syndrome under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

- **Serotonergic Drugs**: Potential pharmacologic interaction (potentially life-threatening serotonin syndrome) with drugs affecting serotonin neurotransmission, including anxiolytics (an anti-anxiety agent that is a nonselective, irreversible inhibitor of serotonin and dopamine transmission) (see Table below). Use with caution. Concurrent administration of serotonin precursors (such as tryptophan) is not recommended. (See Serotonin Syndrome under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

- **Smoking**: Potential pharmacokinetic interaction (reduced duloxetine bioavailability and plasma concentrations). The manufacturer states that routine dosing adjustment is not necessary. However, smokers may experience a small increase in duloxetine dosage (about 15%) in patients who smoke.

- **Theophylline**: Although small increases (averaging from 7-20%) in theophylline AUCs have been reported during concurrent administration of theophylline and duloxetine, combined use of these drugs reportedly has been well tolerated and routine theophylline dosage adjustment does not appear to be necessary during concurrent administration.

- **Thioridazine**: Potential pharmacokinetic (increased plasma thioridazine concentrations) interaction with resulting increased risk of neuroleptic malignant syndrome. The clinical significance of this interaction has not been established by controlled studies of 8-12 weeks’ duration in outpatient settings; it is thought to be related to potentiation of both thioridazine and meperidine in the sacral spinal cord, which increases urethral closure forces and thereby reduces involuntary urine loss.

- **Duloxetine**: Extensively metabolized in the liver; principally via oxidation by the cytochrome P450 (CYP) 2D6 and 2C19 enzymes. Duloxetine is a moderate inhibitor of CYP2D6 and a somewhat weak inhibitor of CYP1A2. The drug is not an inhibitor of CYP2C9, CYP2C19, or CYP3A, nor is it an inducer of CYP1A2 or CYP3A.

### Description

Duloxetine hydrochloride is a selective serotonin- and noradrenaline-reuptake inhibitor (SNRI). It is an antidepressant and anxiolytic agent. The drug has demonstrated analgesic activity in animal models of chronic and persistent pain and in clinical trials evaluating the drug’s activity in conditions associated with chronic pain (e.g., neuropathic pain, fibromyalgia). Duloxetine hydrochloride is pharmacologically related to venlafaxine hydrochloride and desvenlafaxine succinate.

### Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

#### Duloxetine Hydrochloride

**Oral**

- Capsules, delayed-release (containing enteric-coated pellets)
  - 20 mg (of duloxetine) *Cymbalta*, Lilly
  - 30 mg (of duloxetine) *Cymbalta*, Lilly
  - 60 mg (of duloxetine) *Cymbalta*, Lilly

**Venlafaxine Hydrochloride**

- **Uses**
  - **Major Depressive Disorder**: Venlafaxine hydrochloride, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is a phenethylamine derivative antidepressant and anxiolytic agent.

### Advice to Patients

Risk of suicidality, importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment. FDA recommends providing written patient information (medication guide) explaining risks of suicidality each time the drug is dispensed.