Methylphenidate Hydrochloride

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■ Methylphenidate is a piperidine-derivative CNS stimulant that has pharmacologic actions that are qualitatively similar to those of amphetamines.

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 attention deficit hyperactivity disorder (ADHD). Methylphenidate also is used in the symptomatic treatment of narcolepsy.

■ **Attention Deficit Hyperactivity Disorder** 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, hyperkinetic syndrome of childhood, minimal brain dysfunction) in carefully selected children 6 years of age and older, adolescents, and adults. Although long thought of as a childhood disorder, ADHD is now known to persist into adolescence and/or adulthood in some patients, and adults are increasingly being treated for ADHD. Adults maintaining only some of the manifestations of ADHD are considered by DSM-IV to have ADHD in partial remission. ADHD in adults also has been referred to as simply attention deficit disorder (ADD). Most evidence and experience on the treatment of ADHD has been in children. Almost all studies comparing behavioral therapy versus stimulants alone for ADHD have shown a much stronger therapeutic effect from stimulants than from behavioral therapy.

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 at the higher end for community samples versus school samples. ADHD also 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 versus girls varies between 3:1 to 9:1), this difference may be artifactual and decrease with age, being skewed in part to boys because of referral bias related to disruptive behavior since boys generally exhibit more hyperactive/impulsive symptoms and more conduct and oppositional symptoms than girls. In addition, when DSM-IV rather than earlier criteria are used, more females have been diagnosed with the predominantly inattentive type.

The diagnosis of ADHD should be made using well-tested diagnostic interview methods; neuropsychologic and/or biologic tests are not recommended for routine clinical use, although they may be useful to researchers investigating links between symptoms and underlying attentional processes and brain functions. To help ensure an accurate diagnosis and decrease the variation in how the diagnosis is made, clinicians should employ DSM-IV criteria in the context of their clinical assessment to diagnose ADHD. However, given the lack of methods to confirm the diagnosis of ADHD through other means, clinicians must recognize the limitations of the DSM-IV definitions (e.g., most of the development and testing of DSM-IV occurred in children evaluated in psychiatric settings, there are no clear empiric data supporting the number of items required for the diagnosis, current criteria do not take into account gender differences nor developmental differences in behavior, behavioral characteristics remain subjective and may be interpreted differently). According to DSM-IV criteria, there are 3 subtypes of ADHD: the principally inattentive type (ADHD/I), the principally hyperactive-impulsive type (ADHD/HI), and the combined inattentive and hyperactive-impulsive type (ADHD/C).

There currently are *no* data establishing that ADHD results from brain malfunction. ADHD is a clinical diagnosis; while the diagnosis can be made reliably using interview methods, there currently is no independent valid test for ADHD nor have laboratory tests, physical examination findings, or general medical conditions been established as aiding in the clinical assessment of this disorder. Diagnostic methods employed in the clinical setting have been variable, and the frequency of diagnosis of ADHD varies widely among type of practitioner (primary care and developmental pediatricians, family physicians, child neurologists, psychologists, and psychiatrists). Pediatricians, family physicians, and psychiatrists tend to rely on parent rather than teacher input, and there is a general disconnect between developmental or educational (school-based) assessments and health-related (medical practice-based) services, including poor communication between diagnosticians and those who implement and monitor treatment in schools, and follow-up may be inadequate and fragmented. School-based clinics with a team approach that includes parents, teachers, school psychologists, and other mental health specialists may improve barriers to appropriate identification, evaluation, and intervention as well as access to assessment and treatment. Current formal diagnostic criteria for ADHD were designed principally for diagnosing this disorder in young children. However, the American Psychiatric Association (APA) and others (e.g., American Academy of Child and Adolescent Psychiatry [AACAP]) have developed diagnostic criteria (e.g., DSM-IV) for ADHD to ages extending through adulthood.

ADHD usually is characterized by developmentally inappropriate symptoms (e.g., moderate to severe distractibility, short attention span, hyperactivity, emotional lability, impulsivity, carelessness, accident-proneness, irresponsibility, failure to complete tasks). The essential feature of ADHD is a persistent pattern of inattention and/or hyperactivity/impulsivity that is more frequent and severe than is observed in individuals with a comparable developmental level, and core symptoms include developmentally inappropriate levels of attention and concentration, activity, distractability, and impulsivity. Some hyperactive/impulsive or inattentive symptoms are present before 7 years of age, 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 grammar (grade) school. Some impairment from symptoms is present in at least 2 settings (e.g., at home, school, or work), and there is clear evidence of interference with developmentally appropriate social, academic, and/or occupational functioning. The final diagnosis of this disorder should not be made if these symptoms are of only comparatively recent origin. Nonlocalizing (soft) neurologic signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted.

Children with ADHD usually exhibit pronounced difficulties and impairment resulting from the disorder across multiple settings (at school, at home, with peers) as well as resultant long-term adverse effects on later academic, vocational, social-emotional, and psychiatric outcomes. Such children exhibit higher accident rates, and later in life, those with ADHD that is combined with conduct disorders exhibit drug abuse, antisocial behavior, and accidents of all sorts; for many individuals, the long-term effects of ADHD continue into adulthood. Individuals with a history of ADHD consume a disproportionate share of resources and attention from health-care services, the criminal justice system, schools, and other social services, and ADHD, often combined with coexisting conduct disorders, contributes to societal problems including violent crime and teenage pregnancy. Parents of children with ADHD, as with other behavioral disorders and chronic diseases, experience increased levels of parental frustration, marital discord, divorce, and costs for medical care that may not be covered by health insurance. Up to 80% of diagnosed hyperactive children continue to exhibit features of ADHD into adolescence and up to 65% into adulthood, and most experts consider it a chronic disorder that often seems to require ongoing treatment. As a result, ADHD represents a major public health problem with profound impact on individuals, families, schools, and society; however, because there currently are no established means for preventing this disorder, current efforts must be aimed at effectively identifying, diagnosing, and treating ADHD. Comorbid conditions are present in up to two-thirds of clinically referred children with ADHD, including high rates for oppositional defiant disorder, conduct disorder, mood disorders (e.g., depression), and anxiety disorders. Tourette's syndrome and chronic tic disorder also often are present, and speech and language delays are common.

Although some patients continue to experience the full range of ADHD symptoms into adulthood, the occurrence of adult-onset ADHD is unlikely; however, unrecognized cases of ADHD may not be diagnosed until adulthood. A clinical diagnosis of ADHD in adults, according to DSM-IV criteria, requires evidence of symptom onset before 7 years of age, persisting from childhood until the time of evaluation, and with distress and/or impairment in functioning occurring in more than one setting (e.g., home, work). Some symptoms of disinhibition may present differently in adults than children; the physical symptoms of hyperactivity in children may be replaced in adults with fidgetiness or an inner feeling of restlessness, difficulty relaxing, and a feeling of being chronically "on edge". The DMS-IV criteria also state that a diagnosis of ADHD in partial remission may be used for adults who no longer meet the full range of diagnostic criteria that was present in childhood, but still retain some of the manifestations that cause functional impairment. Confirmation of ADHD in previously undiagnosed adults may present challenges such as difficulty in obtaining a longitudinal history, poor insight and underestimation of the severity of symptoms and resulting impairment, and differentiation from other psychiatric conditions (e.g., bipolar disorder, depression, axis II personality disorders, learning disabilities, narcolepsy, undiagnosed borderline intellectual functioning). Rating scales such as the Wender Utah Rating Scale, Brown Attention-Deficit Disorder Scale for Adults, and the Conners Adult ADHD Rating Scale may be useful adjuncts to clinical assessment in confirming the diagnosis of ADHD in adults.

Therapeutic Considerations **Considerations In Choosing a Therapy.** The choice of therapeutic intervention(s) for ADHD will depend on comorbid conditions, specific target symptoms, and the strengths and weaknesses of the patient, family, school, and community. Parents, school personnel, and patients should be included in discussions of 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, pemoline [no longer commercially available in the US]), psychotropic drugs (e.g., antidepressants such as desipramine or imipramine), and other drugs (e.g., atomoxetine, clonidine); psychosocial treatment; dietary management; herbal and homeopathic treatments; biofeedback; meditation; and perceptual stimulation/training. Drug therapy and psychosocial interventions have been the focus of research to date, and efficacy studies have focused principally on the combined-type of ADHD; meeting criteria for inattention and hyperactivity/impulsivity; most randomized trials have been of short duration (usually not exceeding 3 months), although a large, multicenter study with a treatment duration of 14 months recently was reported. Current evidence from these studies 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 on educational and occupational achievements, involvement with police, or other areas of social functioning. Results of 3 double-blind clinical studies in 416 children 6–

12 years old with ADHD indicate that therapy with methylphenidate hydrochloride extended-release trilayer core tablets (Concerta®) was more effective than placebo in decreasing hyperactive-impulsive or inattentive symptoms based on evaluation by community school teachers using the Inattention/Overactivity with Aggression (IOWA) Conners scale. Stimulant drug therapy generally appears to be more effective than psychosocial therapy overall, including behavioral treatment that includes parent training, intensive child-focused treatment, and school-based interventions.

Drug therapy is not indicated in all children with ADHD, and such therapy should be considered only after a complete evaluation including medical history has been performed. The decision to use stimulants should depend on the age of the child and the physician's assessment of the severity and duration of symptoms and should not depend solely on one or more behavioral characteristics. The decision to initiate drug therapy is based on the diagnostic evidence 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-to-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. Stimulants (e.g., methylphenidate, amphetamines) remain the drugs of choice for the management of ADHD. Methylphenidate is the most extensively studied and frequently prescribed drug for the treatment of ADHD. Few, if any, differences have been found between methylphenidate, dextroamphetamine, or pemoline (no longer commercially available in the US) or various dosage forms (short-, intermediate, or long-acting formulations) of the drugs in short-term clinical studies in children with ADHD, and the choice of stimulant therapy should be individualized. However, because hepatic toxicities have been associated with pemoline, some experts recommended its use *only* in patients who failed to respond to adequate trials of methylphenidate *and* an amphetamine as well as adequate trials of second-line therapies (e.g., tricyclic antidepressants, bupropion). In 2005, the US Food and Drug Administration (FDA) determined that the risk of hepatic toxicity associated with the drug outweighs its benefits.

Short-term and longer-term (up to 14 months' duration) studies have shown unequivocal beneficial effects of the stimulants on the defining core symptoms of ADHD (attention and concentration, activity, distractability, 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 will respond to a single stimulant without major adverse effect if therapy is titrated carefully. Children who fail to show positive therapeutic effects or who experience intolerable adverse effects with one stimulant should be tried on an alternative stimulant since most such children will exhibit a positive response to alternative stimulants and current evidence from crossover studies supports the efficacy of different stimulants in the same child; likewise, children who fail an adequate trial of 2 stimulants, should be tried on a third type or formulation of stimulant. Another consideration for trials with alternative stimulants before resorting to a trial with an alternative therapeutic class is the fact that there currently is greater evidence for the safety and efficacy of stimulants in children with ADHD. However, stimulants usually do not normalize the entire spectrum of behavioral problems, and many children effectively treated with these drugs still manifest a higher level of some behavioral problems than children without ADHD or other behavior disturbances. In addition, titration of therapy may result in improvement in one area of functioning while eliciting no or even a detrimental effect in another area. Although stimulants have been shown to remain effective over many years, long-term benefits remain to be established.

Effects on attentional, academic, behavioral, and social domains exhibit substantial interindividual and intraindividual variation, and the principal disappointment with stimulant drug therapy has been the finding that despite improvement in core symptoms of ADHD, there is little consistent improvement in academic or social skills. Stimulants appear to be as effective in patients with ADHD and associated aggression as in those with pure ADHD. It currently is unclear whether patients with comorbid anxiety disorders respond as well to stimulants as other patients with ADHD; however, some evidence suggests that the emphasis for patients with comorbid anxiety should be on increased reliance on psychosocial interventions. For patients whose symptoms are not severe outside the school setting, drug holidays may be attempted for all or part of the summer to assess continuing efficacy and need for such therapy as well as to minimize adverse effects.

Although the abuse potential of stimulants such as amphetamines and methylphenidate is well established, there currently is no evidence that drug abuse is a major problem with properly monitored stimulant therapy for ADHD. In addition, while it has been suggested that the substantial increase in stimulant prescriptions for ADHD in recent years may pose societal risks, the thresbold of drug availability that can lead to oversupply and resultant illicit use is unknown, and there is little evidence that current levels of stimulant production in the US have had a substantial effect on abuse. Drug abuse and cigarette smoking are associated with childhood ADHD, but there has been controversy whether therapy with stimulants increases or decreases the risk of abuse. Some evidence, including a pooled analysis of available prospective and retrospective studies that included information on stimulant use in children, adolescents, and adults with ADHD, indicates that stimulant use does not lead to an increased risk of substance experimentation, use, dependence, or abuse, and effective ADHD stimulant therapy actually may reduce the risk for subsequent drug and alcohol use disorders. Caution in prescribing stimulants may be indicated in patients with comorbid conduct disorder, preexisting dependency, or a chaotic family. If the risk of drug abuse by the patient or their peers or family is considered high, a nonstimulant drug may be preferable to methylphenidate or an amphetamine (e.g., dextroamphetamine).

Multimodal Therapy. Although multimodal therapy, integrating drug therapy with environmental, educational, psychotherapeutic, and school-based approaches, seems intuitively powerful and some studies and clinicians have suggested the superiority of such an approach versus drug therapy or psychosocial interventions, there currently is little evidence from well-designed studies substantiating this assertion, particularly outside a research setting. In addition, data from a large, well-designed study indicates that drug therapy employing systematic intensive monitoring methods over a period of about 1 year is superior to an intensive set of behavioral treatments on core ADHD symptoms; combined behavioral and drug therapy added little benefit overall but did result in greater improvements in social skills and was judged more favorably by parents and teachers. While it remains to be determined, however, whether the addition of behavioral therapy can improve functioning at reduced stimulant dosages, evidence from this study indicates significantly lower total daily dosages of methylphenidate during combined therapy compared with drug therapy alone.

Alternatives to Stimulants. For patients who are intolerant of or unresponsive to stimulants, various other drugs (e.g., tricyclic antidepressants, atomoxetine, bupropion, selective serotonin-reuptake inhibitors, clonidine, guanfacine) have proven useful in clinical practice. However, experience with such alternative drug therapy is far less extensive than with stimulants, and conclusions regarding relative efficacy currently cannot be made.

Most experts recommend use of a tricyclic antidepressant or bupropion for the treatment of ADHD in children who are nonresponsive or partial responders to adequate trials with at least 2 different stimulants. There currently are no data establishing that one of these alternative drugs is more efficacious than the other 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 a causal relationship has not been established, several recent cases of sudden death in children receiving desipramine have raised concerns about the use of this tricyclic. (See Cautions: Pediatric Precautions in Desipramine 28:16.04.28.) Therefore, some experts no longer recommend use of desipramine for the treatment of ADHD in children. Tricyclic antidepressants appear to be less effective than stimulants in improving attentional and cognitive symptoms, but may be useful for impulsive or hyperactive behavior. Tricyclic antidepressant therapy may be indicated as second-line therapy in patients who do not respond to stimulants or who develop clinically important depression or otherwise do not tolerate the drugs; these antidepressants also may be useful for patients with tics or Tourette's disorder or in whom these conditions are exacerbated or not adequately controlled during stimulant therapy. Regardless of which tricyclic antidepressant is considered for use in the management of ADHD, the drugs should be used only if clearly indicated and with careful monitoring, including baseline and subsequent determinations of ECG and other parameters.

Atomoxetine, a selective norepinephrine-reuptake inhibitor, is used in the treatment of ADHD in children 6 years of age and older, adolescents, and adults. Efficacy of atomoxetine for this indication was established in short-term controlled clinical studies in children and adolescents 6–18 years of age and in adults who met DSM-IV criteria for ADHD; efficacy also was established in one longer-term (12 months) controlled clinical study in children and adolescents 6–15 years of age. In one of the short-term studies, atomoxetine and methylphenidate produced comparable results in the reduction of ADHD symptoms in children and adolescents; however, further evaluation in placebo-controlled clinical studies are needed to determine comparative efficacy and tolerance of atomoxetine and other therapies in the treatment of ADHD.

Therapeutic Considerations for Patients with Comorbid Conditions. Alternative drug therapies also may be used alone or in combination with stimulants in patients with ADHD and comorbid conditions (e.g., aggression, anxiety, depression, tic disorders) that are unresponsive to stimulants alone. For the management of anxiety or depression in children with ADHD, selective serotonin-reuptake inhibitors (SSRIs) are considered by some experts the drugs of choice usually to be used in combination with a stimulant. In one clinical study, combined use of methylphenidate and fluoxetine in 32 children with ADHD and a comorbid mood or conduct disorder resulted in marked improvement in school grades and behavior as rated by parents, with no serious adverse effects reported. However, some experts recommend a conservative approach to such combined use of these drugs because of suggestions of rare but potentially serious drug interactions between SSRIs and stimulants. (See Drug Interactions: Antidepressants.)

Some experts state that in the absence of contraindications, α-adrenergic agents (e.g., clonidine) are considered the drugs of choice for the treatment of tic disorders in children with ADHD who were intolerant of stimulants. Clonidine's use has been documented principally in children with ADHD and comorbid conditions, especially sleep disturbances. Antipsychotic agents (e.g., haloperidol, pimozide, risperidone) are recommended by some experts as alternative therapies.

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 α-adrenergic agonist, also has been used in the management of comorbid aggressive symptoms as an adjunct to methylphenidate therapy; however, this use is controversial and further study is needed to evaluate efficacy of such concomitant therapy 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 established. In one controlled study, use of the drug failed to reduce aggression in children. Further studies are needed to evaluate the relative 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 possible risk of withdrawal and tardive dyskinesia. However, 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 age-related differences in response remain to be elucidated. Children and adults appear to share a similar treatment-responsive, underlying disorder. Although reported rates of stimulant efficacy have varied widely in adults, this variation may have resulted from use of inadequate dosages, diagnostic differences, and/or high rates of comorbid disorders. 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 senile behavior and mild depression, but the drug should not be used in the treatment of endogenous depression or agitated depressive 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 choking. (See Precautions Associated with Specific Methylphenidate Formulations 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 (Metadate® 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 sprinkle/applesauce mixture should be taken immediately; the sprinkle/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 sprinkle/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 tablet-like substance in their stools; this is normal since the tablet containing the drug is designed to remain intact and slowly release the drug 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 enhancing techniques are utilized.

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

The methylphenidate transdermal system should be applied once daily in the morning, 2 hours before an effect is needed, and 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 hip that is not oily, damaged, or irritated; application of the transdermal system to the waistline or to areas under tight clothing should be avoided, since clothing may cause the system to rub off. 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 (e.g., opposite hip) 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 replaced with a new system applied at a different site, but the total wear time should not exceed 9 hours per day.

After removal, used systems should be folded so that the adhesive side adheres to itself and then should 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 their packaging, separated from the protective liner, folded so that the adhesive side adheres to itself, and then 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 each transdermal system was applied and removed. If a system was removed without the parent's or caregiver's knowledge, or if a system is missing from the tray, the parent or caregiver should be encouraged to ask the child when and how the system was removed.

■ **Dosage** Dosage of methylphenidate hydrochloride must be carefully adjusted according to individual requirements and response. The extended-release tablets should not be used for initiating therapy nor until the daily dosage is titrated using the conventional tablets; the extended-release tablets may 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 capsules or the extended-release trilayer core tablets for patients who are not currently taking methylphenidate starting with the lowest daily dose and increasing at approximately weekly intervals.

Patients receiving intermediate- or long-acting preparations also may require supplemental therapy with methylphenidate conventional tablets to increase the efficacy, particularly in the morning, or to extend the duration of therapeutic effects later in the day.

Attention Deficit Hyperactivity Disorder Methylphenidate hydrochloride dosage for the treatment of attention deficit hyperactivity disorder (ADHD) should be individualized based on patient response and tolerance. The first dosage that produces an observable response may not be the optimum dosage to improve function, and titration to higher dosages should continue in an attempt to achieve a better response. Such a strategy may require subsequent lowering of dosage when higher dosages produce adverse effects or no further clinical improvement. The best dosage for a given patient is the one that provides optimum therapeutic effects with minimal adverse effects. Dosing schedules also may vary, although there currently are no consistent controlled studies comparing alternative dosing schedules. Patients who require relief only during school may respond adequately to a 5-day (i.e., school day) regimen while those requiring relief at home and school may need a daily regimen throughout the week.

The optimum duration of treatment with methylphenidate has not been established; however, pharmacologic treatment may be required for extended periods. The long-term usefulness of the drug should be reevaluated periodically in patients receiving methylphenidate for extended periods. In patients who have responded to methylphenidate therapy, the drug should be discontinued periodically to assess the patient's condition; improvement may be maintained temporarily or permanently after the drug is discontinued.

Immediate-release Oral Preparations. As an adjunct in the treatment of ADHD in children 6 years of age and older, the usual initial dosage of methylphenidate hydrochloride as conventional (immediate-release) preparations is 5 mg before breakfast and lunch. Dosage may be increased by 5–10 mg daily at weekly intervals and can be administered in twice- or thrice-daily regimens. Although some clinicians have recommended weight-based dosing in children, dosage of methylphenidate, unlike most drugs, generally can be adjusted without regard to the child's weight. When weight-based dosing was employed, an initial dosage of 0.25 mg/kg daily was used. If adverse effects were not observed, the daily dose could be doubled each week until the optimum dosage of 2 mg/kg daily is reached.

Oral dosage in children generally ranges from 5–20 mg 2 or 3 times daily and should not exceed 60 mg daily. Although dosages for older adolescents and adults are similar to those for children, total daily dosages may be increased up to 65 mg since more doses are required to medicate these patients throughout a longer active day. Some clinicians have employed a regimen that included systematic intensive monitoring (referred to as "medical management") in the treatment of ADHD, and such a regimen was shown to be more effective than less intensively titrated and monitored regimens (referred to as "community management"). In the medical management regimen, methylphenidate dosage was titrated over a 28-day period via daily-switch titration involving 5 randomly ordered repeats each of placebo and 5-, 10-, 15-, or 20-mg (higher for children weighing more than 25 kg) daily dosages; each dose was repeated at breakfast and lunch, with a half dose (rounded to nearest 5 mg) given in the afternoon. Based on clinical assessment of response, a best dose was chosen for initial maintenance. In addition to the systematic dosage titration, patients underwent 30-minute monthly drug therapy assessment visits during maintenance. Pharmacotherapists could increase or decrease therapy during such visits by 10 mg daily. In general, patients received higher than typical dosages of the drug when this titration and monitoring method was employed. Dosage at the end of a 14-month study period averaged 37.7 mg daily administered in 3 unequally divided doses daily as noted above.

Children whose dosage is excessive or who are overly sensitive to the drug may become overfocused or appear dull or overly restricted; a dosage reduction may obviate such effects. Rarely, some children may experience psychotic reactions, mood disturbances, or hallucinations at relatively high dosages. If a beneficial effect is not attained after appropriate dosage adjustment over a one-month period, methylphenidate therapy should be discontinued.

Intermediate-acting Oral Preparations. Methylphenidate hydrochloride extended-release tablets (Metadate® 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 controlled with conventional methylphenidate hydrochloride 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 20 mg of methylphenidate hydrochloride extended-release tablets 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 20–40 mg once daily or 40 mg in the morning and 20 mg in the early afternoon.

Long-acting Oral Preparations. Methylphenidate hydrochloride extended-release capsules (Metadate® CD, Ritalin® LA) also may 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 in the morning. Alternatively, when a lower initial daily dosage is appropriate, therapy with Ritalin® LA may be initiated at a dosage of 10 mg once daily. The manufacturer states that Metadate® CD extended-release capsules should be administered before breakfast. Dosage of Metadate® CD may be increased by 10–20 mg daily at weekly intervals, until an optimum response is achieved or adverse effects are observed. Dosage of Ritalin® LA may be increased by 10 mg daily at weekly intervals. Dosages of methylphenidate hydrochloride extended-release capsules exceeding 60 mg daily are not recommended.

Alternatively, as an adjunct in the treatment of ADHD, methylphenidate hydrochloride extended-release trilayer core tablets (Concerta®) may be used. The usual initial dosage of the drug as extended-release trilayer core tablets is 18 mg once daily, in the morning. If adequate response does not occur, dosage may be increased at approximately weekly intervals. The maximum dosage of Concerta® recommended by the manufacturer is 54 mg daily for children 6–12 years of age or 72 mg daily (not to exceed 2 mg/kg daily) for adolescents 13–17 years of age; however, some clinicians state that dosage in children 6–12 years of age may be increased to a maximum dosage of 72 mg daily.

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 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 methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 5 mg twice daily can be switched to a dosage of 10 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 or a 20-mg dosage of an extended-release tablet can be switched to a dosage of 20 mg every morning as Ritalin® LA 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 or a 40-mg dosage of an extended-release tablet can be switched to a dosage of 40 mg every morning as Ritalin® LA extended-release capsules. Patients being transferred from methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 30 mg twice daily or a 60-mg dosage of an extended-release tablet can be switched to a dosage of 60 mg every morning as Ritalin® LA extended-release capsules. For other conventional or extended-release tablet regimens, the nearest daily dosage can be substituted based on clinical judgment.

The manufacturer of Concerta® 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 therapy using a conventional tablet at a dosage of 5 mg 2 or 3 times daily can be switched to a dosage of 18 mg every morning as the extended-release trilayer core tablets. Patients receiving methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 10 mg 2 or 3 times daily can be switched to 36 mg every morning of the methylphenidate hydrochloride extended-release trilayer core tablets. Patients receiving methylphenidate hydrochloride therapy using a conventional tablet at a dosage of 15 mg 2 or 3 times daily can be switched to 54 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 tablets should not exceed 54 mg daily. A 27-mg extended-release trilayer core tablet also is available for patients who require a more gradual titration or who can not tolerate a dosage of 36 mg daily. For other conventional or extended-release tablet regimens, the nearest equivalent daily dosage can be substituted based on clinical judgment. Subsequent titration to higher or lower dosages may be necessary and should occur at approximately weekly intervals, guided by the patient's clinical response and tolerance; however, the manufacturer states that daily dosages exceeding 72 mg are not recommended.

In some patients receiving long-acting methylphenidate preparations, supplemental doses of a short-acting (conventional) preparation may be needed.

Transdermal System. Dosage titration, final dosage, and wear time of the transdermal system should be individualized according to the needs and response of the patient.

The recommended initial dosage of methylphenidate in patients who are receiving the transdermal formulation as their initial methylphenidate regimen is 1 system delivering 10 mg/9 hours applied once daily. If adequate response is not achieved, dosage may be increased at weekly intervals by advancing to the next larger dosage system (i.e., a dosage system delivering 15 mg/9 hours applied once daily during week 2, followed by a dosage system delivering 20 mg/9 hours applied once daily during week 3, and then a dosage system delivering 30 mg/9 hours applied once daily during week 4).

Because differences in bioavailability exist between the methylphenidate transdermal system and other methylphenidate formulations, patients being transferred from therapy with other methylphenidate formulations to transdermal therapy with the drug should receive the same initial transdermal dosage and follow the same dosage titration schedule recommended for patients receiving transdermal methylphenidate as their initial methylphenidate regimen.

The methylphenidate transdermal system may be removed earlier than 9 hours if a shorter duration of effect is desired or if late-day adverse effects occur. If aggravation of symptoms or other adverse events occur, the dosage or wear time should be reduced, or, if necessary, the drug should be discontinued.

Narcolepsy In the treatment of narcolepsy, the usual oral adult dosage of methylphenidate hydrochloride is 10 mg 2 or 3 times daily, given 30–45 minutes before meals. Some patients may require 40–60 mg daily; in others, 10–15 mg daily may be adequate.

Cautions

Methylphenidate generally is well tolerated. Common adverse effects of the drug include nervous system (insomnia, delayed sleep onset, headache, nervousness, jitteriness, social withdrawal) and GI (anorexia) effects. Most adverse effects of methylphenidate can be managed successfully by adjustment in dosage and/or schedule. About 15–30% of children with ADHD experience tics while receiving stimulants such as methylphenidate, but such tics usually are transient. About half of children with ADHD have underlying Tourette's syndrome, and the effects of stimulants on tics are unpredictable; the presence or emergence of tics is not an absolute contraindication to stimulant therapy and some evidence indicates that the incidence of tics is not increased with such therapy.

Discontinuance of methylphenidate therapy, because of sadness and an increase in tics, respectively, was required in 0.9% of patients receiving extended-release trilayer core tablets and 1% of patients receiving placebo in a 4-week controlled study in children. In a 2-week controlled study in adolescents, discontinuance of methylphenidate therapy (because of increased mood irritability) was required in 0% of patients receiving extended-release trilayer core tablets and 1.1 % of patients receiving placebo. In uncontrolled clinical trials, adverse effects requiring discontinuance of methylphenidate therapy occurred in 6.7% of patients receiving the extended-release trilayer core tablets. The principal reasons for discontinuance were insomnia in 1.5% of patients, twitching in 1% of patients, and nervousness, emotional lability, abdominal pain, and anorexia each in 0.7% of patients. Discontinuance of methylphenidate therapy also occurred in 2 patients (1%) receiving extended-release capsules (Metadate® CD) in controlled clinical trials, principally because of rash and pruritus in one patient and headache, abdominal pain, and dizziness in the other patient. In addition, discontinuance of methylphenidate therapy because of depression occurred in a child with ADHD (1.5%) receiving extended-release capsules (Ritalin® LA) in a double-blind controlled clinical trial. Discontinuance also occurred in 6 patients (3.7%) receiving the drug in this trial during the initial single-blind titration period; the reasons for discontinuance were anger (2 patients), hypomania, anxiety, depressed mood, fatigue, migraine, and lethargy. In a 7-week controlled trial in children, adverse effects requiring discontinuance of therapy occurred in 7.1% of patients receiving transdermal methylphenidate and 1.2% of those receiving placebo; reasons for discontinuance of transdermal methylphenidate therapy included erythema or other reactions at the application site, confusional state, crying, headache, irritability, tics, viral infection, or infectious mononucleosis.

Loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently in children than in adults receiving methylphenidate.

■ **Nervous System Effects** The most frequent adverse effects of methylphenidate appear to be dose related and include nervousness and insomnia. Insomnia has been reported in 4–5% of children and adolescents with ADHD receiving methylphenidate hydrochloride extended-release trilayer core tablets, in 5% of children with ADHD receiving Metadate® CD extended-release capsules, in about 3% of children with ADHD receiving Ritalin® LA 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

core tablets and in 12% of children with ADHD receiving extended-release capsules of the drug in clinical trials. Affect lability (including emotionality and emotional sensitivity, instability, and lability) has been reported in 6% of children with ADHD receiving methylphenidate as a transdermal system in clinical trials. Dizziness was reported in 2% of children with ADHD receiving extended-release trilayer core tablets in clinical trials. In 2 uncontrolled studies, the cumulative incidence of new-onset tics in children receiving methylphenidate hydrochloride extended-release trilayer core tablets was reported to be 9% after 27 months of treatment (first study) and 1% after up to 9 months of treatment (second study). Ties 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. Neuroleptic malignant syndrome (NMS) also has been reported rarely in patients receiving methylphenidate; most of these 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 venlafaxine. It is not known if such a reaction was associated with administration of either drug alone or if it represented a drug interaction between methylphenidate and venlafaxine 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 definitely established.

■ **GI and Growth Effects** Abdominal pain and anorexia have been reported in 7 and 2–4%, respectively, of children and adolescents with ADHD receiving methylphenidate hydrochloride extended-release trilayer core 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 also has been reported in about 3% of children with ADHD receiving extended-release capsules (Ritalin® LA) and in 5% of children with ADHD receiving methylphenidate as a transdermal system in controlled clinical trials. Although appetite suppression and weight loss are common with stimulant therapy, there is no apparent difference in their occurrence between methylphenidate or amphetamine (e.g., dextroamphetamine) therapy in children. Results of one study suggest that prolonged methylphenidate hydrochloride therapy (30–40 mg daily) may cause suppression of normal weight gain in children. Results of an analysis of weight and height patterns in children 7–13 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 2.7 kg over 3 years), 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 into adulthood found no significant impairment in height achieved. In general, studies of stimulants in children have found little or no decrease in expected height, with any decrease in growth early in treatment being compensated for later on. Although drug holidays during summers have been suggested to minimize weight loss and other potential adverse effects, there currently are no data from controlled studies establishing whether such holidays are beneficial or associated with risks.

Vomiting was reported in 3–4% and diarrhea was reported in 2% of children and adolescents with ADHD receiving methylphenidate hydrochloride extended-release trilayer core tablets in clinical trials. Nausea and vomiting were reported in 12 and 10%, respectively, of children with ADHD receiving methylphenidate as a transdermal system in clinical trials. Other adverse GI effects of methylphenidate include weight loss during prolonged therapy and dryness of the throat.

■ **Hepatic Effects** Abnormal liver function, ranging from serum aminotransferase (transaminase) elevations to hepatic coma, 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, arthralgia, exfoliative dermatitis, erythema multiforme with histopathologic findings of necrotizing vasculitis, and thrombocytopenic 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 the transdermal system but generally causes minimal or no discomfort.

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 hip). However, because sensitization was not specifically assessed in efficacy studies, the incidence of contact sensitization associated with appropriate use of the transdermal system 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; leukopenia; anemia; and eosinophilia have been reported rarely in patients receiving methylphenidate, but a causal relationship to the drug has not been definitely established. (See Other Precautions and Contraindications under Cautions: Precautions and Contraindications.)

■ **Cardiovascular Effects** Sudden death, stroke, myocardial infarction, angina, tachycardia, cardiac arrhythmias, 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 arteritis and/or occlusion have been reported in patients receiving methylphenidate. Cardiac arrest, 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.

■ **Ocular Effects** Blurred vision and difficulty with accommodation have been reported in patients receiving methylphenidate.

■ **Respiratory Effects** Upper respiratory tract infection, increased cough, pharyngitis, sinusitis, and rhinitis were reported in 8, 4, 2–4, 3, and 3%, respectively, of children and adolescents receiving methylphenidate hydrochloride extended-release trilayer core tablets in clinical trials. Nasal congestion and nasopharyngitis were reported in 6 and 5%, respectively, of children receiving methylphenidate as a transdermal system in clinical trials.

■ **Other Adverse Effects** Pulmonary talc granulomata, superficial abscesses, other foreign body reactions, and eosinophilia have been reported in drug abusers who have dissolved methylphenidate hydrochloride tablets in water and injected the resulting solution.

Scalp hair loss has been reported rarely in patients receiving methylphenidate, but a causal relationship to the drug has not been definitely established.

Dysmenorrhea has been reported in adolescents receiving methylphenidate hydrochloride extended-release trilayer core tablets.

■ **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 onset or worsening of aggressive behavior or hostility.

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 dosages of stimulants. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% of patients receiving usual dosages of stimulants (i.e., 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 discontinuance of therapy may be appropriate.

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 to determine if they are at risk for 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 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., adverse psychiatric effects, possible cardiovascular risks) 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, including suicidal ideation or behaviors of 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 modest increases in average blood pressure (i.e., by about 2–4 mm Hg) and heart rate (i.e., by 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 and heart rate. Caution is advised in patients 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 dosages 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 dosages of CNS stimulants. Results of one retrospective, case-control epidemiologic study showed that there may be an association between use of stimulant medications (e.g., methylphenidate) 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. Amphetamines or other stimulants should not be discontinued 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 amphetamines and other stimulants to evaluate a possible link between 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 evaluating clinical data on approximately 500,000 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., ECG, 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 serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac conditions. Patients who develop exertional chest pain, unexplained syncope, or other manifestations 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., possible 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, including cardiac or cardiovascular 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 under Cautions: Precautions and Contraindications, in the Amphetamines General Statement 28:20.04.

Precautions Associated with Specific Methylphenidate Formulations Administration of methylphenidate hydrochloride chewable tablets without adequate fluid may cause tablet contents to swell, resulting 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 chest pain, 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 warned that each 2.5-, 5-, or 10-mg chewable tablet contains aspartame (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 capsules (Metadate® CD) contain sucrose and should not be used in patients with hereditary fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency.

Methylphenidate hydrochloride extended-release trilayer core tablets generally should not be used in patients with preexisting 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. Release of 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 is suspected (i.e., if erythema develops and is accompanied 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 test sites, or generalized skin eruptions in previously unaffected skin. Other systemic reactions may include headache, fever, malaise, arthralgia, diarrhea, or vomiting. 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, appropriate use) as needed. 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, glaucoma, suicidal ideation or behaviors, mental or psychiatric disorder, seizures, history of substance abuse).

The manufacturers recommend that laboratory tests, including periodic complete blood cell (with differential) and platelet counts, be performed periodically during prolonged methylphenidate hydrochloride therapy. However, the clinical rationale for this precaution has been questioned by some clinicians since adverse hematologic effects have occurred only rarely in patients receiving methylphenidate and a causal relationship to the drug has not been conclusively established in these cases. Most clinicians consider routine hematologic monitoring unnecessary in the absence of clinical signs (e.g., fever, sore throat, 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 hallucinosis can occur, particularly with parenteral abuse. The possibility of psychological or physical dependence should be considered, particularly when methylphenidate is administered to alcoholics, emotionally unstable patients, or those known to have been addicted to other drugs. The drug should be administered with caution to persons with a history of drug or alcohol dependence since such patients may increase dosage on their own initiative.

Abrupt withdrawal of methylphenidate following prolonged administration may unmask severe depression as well as the effects of chronic overactivity; paranoid and suicidal ideation, dysphoric mood (e.g., depression, irritability, anxiety), fatigue, insomnia or hypersomnia, psychomotor agitation, and disturbed sleep also may occur. Therefore, patients should be carefully supervised during withdrawal of the drug; long-term follow-up may be required since some manifestations (e.g., depression) may persist for prolonged periods.

Visual disturbances (difficulty with accommodation, blurred vision) have been reported in patients receiving stimulants, including methylphenidate.

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 a history of seizures, in those with prior EEG abnormalities in the absence 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 appropriate anticonvulsant therapy. If seizures occur in patients receiving methylphenidate, the drug should be discontinued.

Therapy with CNS stimulants may be associated with at least a temporary suppression of growth in children. (See Cautions: GI and Growth Effects.)

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 glaucoma, in patients with motor tics or a family history or diagnosis of Tourette's syndrome, and in those known to be hypersensitive to the drug. However, AAP states that the presence of tics before or during medical management of ADHD is *not* an absolute contraindication to stimulant drug use. (See the opening discussion in Cautions.) Methylphenidate also is contraindicated during or within 14 days of administration of monoamine oxidase (MAO) inhibitors since hypertensive crisis could result. (See Drug Interactions: Antidepressants.)

■ **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 than those reported in older children with

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 are the lack of 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 a 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, AAP states that studies of stimulants in children generally have found little or no decrease in expected height, with any decrease in growth early 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 usual dosages of CNS stimulants. Results of one retrospective, case-control epidemiologic study suggested a possible association between use of stimulant medications and sudden unexplained 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 dosages 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. Dosage reduction 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 coumarin anticoagulants and anticonvulsants (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 coumarin anticoagulants, the possibility that methylphenidate may raise the serum concentrations of these drugs to toxic concentrations necessitating a decrease in dosage should be considered. Additionally, metabolism of phenylbutazone (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 coumarin anticoagulants, anticonvulsants, or phenylbutazone may be required in patients receiving concomitant methylphenidate therapy. It may be necessary to monitor plasma drug concentrations (or, in the case of coumarin anticoagulants, prothrombin time [PT]) when methylphenidate is initiated or discontinued.

Studies to evaluate the effects of changes in gastric pH on the absorption of methylphenidate hydrochloride administered as extended-release capsules (Ritalin® LA) have not been performed to date; the manufacturer states that concurrent use of drugs that increase gastric pH (e.g., antacids, H_2-receptor antagonists) could potentially alter the release characteristics of the formulation.

Acute Toxicity

■ **Manifestations** Acute toxicity due to methylphenidate overdosage results in symptoms similar to those of acute amphetamine intoxication and may be manifested by cardiovascular symptoms including flushing, palpitation, hypertension, cardiac arrhythmias, and tachycardia. Mental disturbances such as confusion, delirium, euphoria, hallucinations, and toxic psychosis may also occur. Other symptoms of overdosage include agitation, headache, vomiting, dryness of mucous membranes, mydriasis, hyperpyrexia, sweating, tremors, hyperreflexia, muscle twitching, and seizures which may be followed by coma.

■ **Treatment** In the treatment of methylphenidate overdosage, general physiologic supportive measures, including maintenance of adequate circulation and respiratory exchange should be immediately instituted. The patient should be protected against self-injury and should be isolated to avoid possible external stimuli. In cases of overdosage involving transdermal methylphenidate, all transdermal 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, gastric contents may be evacuated 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 for the treatment of hyperpyrexia. Effectiveness of peritoneal dialysis or extracorporeal hemodialysis for the treatment of methylphenidate overdosage has not been established.

Pharmacology

The pharmacologic actions of methylphenidate are qualitatively similar to those of the amphetamines and include CNS and respiratory 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 thalamus; stimulation by methylphenidate causes an increase in 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%), which suggests substantial first-pass metabolism. Following oral administration of methylphenidate hydrochloride as conventional tablets, oral solution, or chewable tablets, peak plasma concentrations were attained at approximately 1–2 hours. Methylphenidate hydrochloride oral solution and chewable tablets are bioequivalent to methylphenidate hydrochloride conventional tablets.

Extended-release methylphenidate hydrochloride tablets are absorbed more slowly but to the same extent as the conventional tablets. Following oral administration of methylphenidate hydrochloride extended-release tablets (Methylin® ER, Ritalin-SR®) in children, peak plasma concentrations were attained at 4.7 hours.

After oral administration of methylphenidate hydrochloride 20 or 40 mg as extended-release capsules (Metadate® 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 (AUC) for methylphenidate were slightly lower following administration of 20 mg of the drug once daily as Metadate® 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 administered once 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 and second peak plasma concentrations were similar following administration of 40 mg of the drug once daily as Ritalin® LA extended-release capsules or 20 mg twice daily (given 4 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 with the extended-release capsules. In adults, the 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, an initial peak plasma concentration is attained within 1 hour while peak plasma concentrations of about 3.7 ng/mL are achieved within approximately 6–10 hours.

Following application of a single transdermal system (Daytrana®), peak plasma methylphenidate concentrations are attained within 7.5–10.5 hours. Application of the transdermal system to inflamed skin results in 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 occurs 0.5 hour earlier, and median peak plasma concentration and AUC are twofold and 2.5-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 with chronic administration.

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., Metadate® ER, Methylin® ER, Ritalin-SR®), and about 8–12 hours after oral administration of extended-release trilayer core tablets (Concerta®) or extended-release capsules (e.g., Metadate® CD, Ritalin® LA).

Because of substantially greater first-pass metabolism following oral compared with transdermal administration, a lower transdermal dose of methylphenidate may result in greater systemic exposure to *d*-methylphenidate (the more pharmacologically active isomer) than a higher (on a mg/kg basis) oral dose of the drug. Following repeated transdermal administration of methylphenidate, *l*-methylphenidate is systemically available; on average, systemic exposure to *l*-methylphenidate is 27–45% less than exposure to *d*-methylphenidate. Little, if any, *l*-methylphenidate is systemically available following oral administration of the drug.

In adults, administration of methylphenidate hydrochloride 20 mg as an oral solution with a high-fat meal delayed the peak plasma concentration by approximately 1 hour and increased the average peak plasma concentration and AUC for methylphenidate by 13 and 25%, respectively; the magnitude of increase in peak plasma concentration and AUC is similar between methylphenidate hydrochloride oral solution and conventional tablets. Administration of methylphenidate hydrochloride 20 mg as chewable tablets with a high-fat meal in adults delayed the time to peak plasma concentration by approximately 1 hour and increased the AUC by about 20%; the magnitude of food effect is comparable to that observed with conventional tablets. Administration of methylphenidate hydrochloride 40 mg as extended-release capsules (Metadate® CD) with a high-fat meal in adults delayed the first peak plasma concentration by approximately 1 hour and increased the average peak plasma concentration and AUC for methylphenidate by 30 and 17%, respectively. In a single-dose study in healthy adults, administration of Ritalin® LA extended-release capsules with a high-fat breakfast delayed the first and second peak plasma concentrations and decreased the second mean peak plasma concentration by 25% compared with administration in the fasting state. However, the bioavailability of the extended-release capsules (i.e., Metadate® CD, Ritalin® LA) was not affected by opening the capsules and sprinkling the contents onto applesauce.

■ **Distribution** The extent of methylphenidate distribution in humans is unknown.

■ **Elimination** Methylphenidate is metabolized primarily by de-esterification to form α-phenylpiperidine acetic acid (ritalinic acid), which has little or no pharmacologic activity. Some data indicate that clearance of methylphenidate increases with increasing weight, suggesting that patients with higher body weight may have lower exposures to total methylphenidate at similar doses.

Following oral administration of methylphenidate hydrochloride conventional tablets in adults or children, the mean terminal elimination half-life was reported to be 3.5 or 2.5 hours, respectively. The mean terminal elimination half-life following oral administration of methylphenidate hydrochloride as an oral solution in adults is similar to that following administration of conventional tablets. The mean terminal half-life following oral administration of methylphenidate hydrochloride 20 mg as chewable tablets in adults is 3 hours, which is comparable to that following administration of conventional tablets. Following oral administration of methylphenidate hydrochloride conventional (5 mg 3 times daily) or extended-release trilayer core tablets (Concerta®) (18 mg once daily) in adults, the plasma elimination half-life reportedly is 3 or 3.5 hours, respectively. Following oral administration of a single 20-mg dose of methylphenidate hydrochloride as extended-release capsules (Metadate® CD) in adults, the mean terminal half-life of the drug was reported to be 6.8 hours. The mean elimination half-life of methylphenidate following removal of the transdermal system in children 6–12 years was approximately 3–4 hours for *d*-methylphenidate and 1.4–2.9 hours for *l*-methylphenidate.

Following oral administration of 20 mg of radiolabeled methylphenidate hydrochloride as conventional tablets, approximately 50, 80, and 95% of the dose was recovered as metabolites in urine within 6, 24, and 90 hours, respectively.

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 formulated for immediate release of the drug; extended-release tablets (e.g., Metadate® ER, Methylin® ER, Ritalin-SR®) with an intermediate duration of action; and extended-release capsules (e.g., Metadate® CD, Ritalin® LA) and extended-release tablets (e.g., Concerta®) with a longer duration of action. Methylphenidate is commercially available as a transdermal system.

The commercially available methylphenidate hydrochloride extended-release capsules (Metadate® CD) contain 30% of the dose in immediate-release pellets and 70% of the dose in extended-release pellets that slowly release methylphenidate. The commercially available methylphenidate hydrochloride extended-release capsules (Ritalin® LA) contain the drug in equal amounts in immediate- and extended-release pellets.

The commercially available extended-release tablets of methylphenidate hydrochloride (Concerta®) contain the drug in an oral osmotic delivery system formulation. The osmotic delivery system consists of an osmotically active trilayer core (comprised of two layers containing the drug and a push layer containing osmotically active components) surrounded by a semipermeable membrane with an immediate-release drug overcoat and a laser-drilled delivery orifice. When exposed to water in the GI tract, the drug overcoat is solubilized providing an initial dose of methylphenidate; as water enters the formulation, the osmotic layer expands and the drug is pushed out the delivery orifice of the membrane into the GI tract at a controlled rate. The rate of methylphenidate delivery in the GI tract is independent of GI pH or the presence of food in the GI tract. The inert tablet ingredients remain intact and are eliminated in feces.

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.

■ **Stability** Methylphenidate hydrochloride tablets, extended-release tablets, extended-release trilayer core tablets (Concerta®), and extended-release capsules (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.

Preparations

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.

Methylphenidate

Topical		
Transdermal System	10 mg/9 hours (27.5 mg/12.5 cm²)	**Daytrana®** (C-II), Shire
	15 mg/9 hours (41.3 mg/18.75 cm²)	**Daytrana®** (C-II), Shire
	20 mg/9 hours (55 mg/25 cm²)	**Daytrana®** (C-II), Shire
	30 mg/9 hours (82.5 mg/37.5 cm²)	**Daytrana®** (C-II), Shire

Methylphenidate Hydrochloride

Oral		
Capsules, extended-release (containing beads)	10 mg (beads, extended-release 7 mg with 3 mg immediate-release)	**Metadate® CD** (C-II), UCB
	10 mg (beads, extended-release 5 mg with 5 mg immediate-release)	**Ritalin® LA** (C-II), Novartis
	20 mg (beads, extended-release 14 mg with 6 mg immediate-release)	**Metadate® CD** (C-II), UCB
	20 mg (beads, extended-release 10 mg with 10 mg immediate-release)	**Ritalin® LA** (C-II), Novartis
	30 mg (beads, extended-release 21 mg with 9 mg immediate-release)	**Metadate® CD** (C-II), UCB
	30 mg (beads, extended-release 15 mg with 15 mg immediate-release)	**Ritalin® LA** (C-II), Novartis
	40 mg (beads, extended-release 28 mg with 12 mg immediate-release)	**Metadate® CD** (C-II), UCB
	40 mg (beads, extended-release 20 mg with 20 mg immediate-release)	**Ritalin® LA** (C-II), Novartis
	50 mg (beads, extended-release 35 mg with 15 mg immediate-release)	**Metadate® CD** (C-II), UCB
	60 mg (beads, extended-release 42 mg with 18 mg immediate-release)	**Metadate® CD** (C-II), UCB
Solution	5 mg/5 mL	**Methylin® Oral Solution** (C-II), Sciele
	10 mg/5 mL	**Methylin® Oral Solution** (C-II), Sciele
Tablets	5 mg*	**Methylin®** (C-II), Mallinckrodt
		Methylphenidate Hydrochloride Tablets (C-II)
		Ritalin® Hydrochloride (C-II), Novartis
	10 mg*	**Methylin®** (C-II; scored), Mallinckrodt
		Methylphenidate Hydrochloride Tablets (C-II)
		Ritalin® Hydrochloride (C-II; scored), Novartis

	20 mg*	Methylin* (C-II; scored), Mallinckrodt
		Methylphenidate Hydrochloride Tablets (C-II)
		Ritalin* Hydrochloride (C-II; scored), Novartis
Tablets, chewable	2.5 mg	Methylin* (C-II), Sciele
	5 mg	Methylin* (C-II), Sciele
	10 mg	Methylin* (C-II; scored), Sciele
Tablets, extended-release	10 mg	Metadate* ER (C-II), UCB
		Methylin* ER (C-II), Mallinckrodt
	20 mg*	Metadate* ER (C-II), UCB
		Methylin* ER (C-II), Mallinckrodt
		Methylphenidate Hydrochloride Tablets (C-II)
		Ritalin-SR* (C-II), Novartis
Tablets, extended-release core	18 mg (core 14 mg with 4 mg immediate-release)	Concerta* (C-II), McNeil
	27 mg (core 21 mg with 6 mg immediate-release)	Concerta* (C-II), McNeil
	36 mg (core 28 mg with 8 mg immediate-release)	Concerta* (C-II), McNeil
	54 mg (core 42 mg with 12 mg immediate-release)	Concerta* (C-II), McNeil

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Modafinil

■ 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 weakness (cataplexy) while awake and disrupted nocturnal 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 9 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 Steer Clear Performance Test [SCPT]) 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 overall disease status (measured by the Clinical Global Impression of Change [CGI-C]). However, despite the clinical improvement, 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 improvement in overall disease status on the CGI-C in the two 9-week studies establishing efficacy in the US was 60–72, 58–64, or 37–38% for the 400-mg regimen, 200-mg regimen, or placebo, respectively. The efficacy of the 2 modafinil dosage regimens was not shown to differ significantly in these studies.

Although the long-term efficacy of modafinil has not been established systematically beyond 9 weeks, improvements in overall disease status on the CGI-C and in subjective measures of sleepiness on the ESS were maintained in a 40-week open-label extension of one of the trials. In this open-label extension, the percentage of patients exhibiting improvement on the CGI-C ranged from 84% after 2 weeks of extension therapy to 91% after 40 weeks. The drug also was 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 establishing efficacy in the US had histories of cataplexy, those requiring anticataplectic therapy generally were excluded from enrollment. Therefore, current evidence of efficacy for modafinil is limited principally to 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 voluntarily sleep (nap) during the daytime. Like other CNS stimulants modafinil can alter mood, perception, thinking, and feelings and can cause psychoactive 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 reinforcing; however, the somatic effects of the drug were comparable to those of caffeine and differed from those of amphetamine. Although there currently does not appear to be evidence of problems with modafinil abuse, caution is recommended in patients with a history of drug or stimulant abuse. Withdrawal of modafinil has not been associated with any manifestations of dependency.

■ **Obstructive Sleep Apnea/Hypopnea Syndrome** Modafinil is used in the symptomatic treatment of OSAHS to improve wakefulness in adults with excessive sleepiness. The drug should be used as an adjunct to standard treatment(s) for the underlying obstruction (e.g., nasal continuous positive airway pressure [CPAP]). If CPAP is considered the treatment of choice for a patient with OSAHS, every effort should be made to optimize CPAP treatment for an adequate period of time prior to initiating modafinil therapy. When modafinil is used adjunctively with CPAP treatment, the encouragement of and periodic assessment of CPAP compliance is necessary.

Efficacy of modafinil in reducing excessive daytime sleepiness in patients with OSAHS was established principally in 2 multicenter, placebo-controlled clinical trials. In both of these studies, enrolled patients met the International Classification of Sleep Disorders (ICSD) criteria for OSAHS, which also are consistent with DSM-IV criteria. These criteria include either excessive sleepiness or insomnia with frequent episodes of impaired breathing during sleep and associated features (e.g., loud snoring, morning headaches, dry mouth upon awakening) or polysomnography demonstrating more than 5 obstructive apneas (each greater than 10 seconds in duration) per hour of sleep and one or more of the following: frequent arousals from sleep associated with the apneas; bradytachycardia; and arterial oxygen desaturation in association with the apneas. In addition, all patients enrolled in these studies had excessive daytime sleepiness as demonstrated by a score of 10 or higher on the Epworth Sleepiness Scale (ESS) despite treatment with CPAP. Evidence that CPAP was effective in reducing the episodes of apnea/hypopnea also was required along with documentation of CPAP use.

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 fully compliant with CPAP (defined as CPAP use for more than 4 hours per night on more than 70% of nights); the remainder of patients were partially CPAP compliant (defined as CPAP use for less than 4 hours per night on more than 30% of nights). Efficacy of modafinil was principally evaluated by measurement of sleep latency as assessed by the Maintenance of Wakefulness Test (MWT) and change in the patient's overall disease status as measured by the Clinical Global Impression of Change (CGI-C) at week 12 or 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 70% of nights) was required for all patients. Efficacy in reducing daytime sleepiness was principally assessed by the change from baseline on the ESS at week 4 or the final visit. Patients who received modafinil demonstrated a significant reduction in their ESS score from baseline (mean scores reduced by 4.6) compared with patients receiving placebo (mean scores reduced by 2). In addition, the percentage of patients with normalized daytime sleepiness (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 compared with baseline following 3, 6, 9, and 12 months of 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 chronic SWSD (which are consistent with DSM-IV criteria for circadian rhythm sleep disorder: shift work type) require a primary complaint of excessive sleepiness or insomnia that is temporally associated with a work period

ommends avoiding concomitant alcohol consumption during desvenlafaxine therapy.

■ **Electroconvulsive Therapy** The risks and/or benefits of combined use of electroconvulsive therapy and desvenlafaxine have not been evaluated.

Description

Desvenlafaxine succinate, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is an antidepressant. Desvenlafaxine is the principal active metabolite of venlafaxine and is pharmacologically related to duloxetine, another SNRI.

The exact mechanism of antidepressant action of desvenlafaxine has not been fully elucidated but appears to be associated with the drug's potentiation of serotonergic and noradrenergic activity in the CNS. Like venlafaxine and duloxetine, desvenlafaxine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake; however, inhibition of dopamine reuptake at concentrations that inhibit serotonin and norepinephrine reuptake appears unlikely in most patients. The drug does not inhibit monoamine oxidase (MAO) and has not demonstrated significant affinity for muscarinic cholinergic, H_1-histaminergic, α_1-adrenergic, dopaminergic, γ-aminobutyric acid (GABA), glutamate, and opiate receptors in vitro.

Desvenlafaxine is principally metabolized via conjugation by uridine diphosphoglucuronosyltransferase (UGT) isoenzymes and, to a lesser extent, through oxidation (by the cytochrome P-450 [CYP] 3A4 isoenzyme). The drug minimally inhibits the CYP2D6 isoenzyme and does not inhibit the CYP 1A2, 2A6, 2C8, 2C9, or 2C19 isoenzymes. Desvenlafaxine is not an inhibitor of CYP3A4, nor is it an inducer of CYP3A4. The drug exhibits a low degree of protein binding (30%) and has a mean elimination half-life of approximately 11 hours. Approximately 45% of a single oral dose of desvenlafaxine is eliminated unchanged in the urine at 72 hours, approximately 19% of the dose is excreted as the glucuronide metabolite, and less than 5% is excreted as the oxidative metabolite (N,O-didesmethylvenlafaxine).

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. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.) FDA recommends providing written patient information (medication guide) explaining risks of suicidality each time the drug is dispensed. Importance of advising patients about importance of reading the patient information before taking desvenlafaxine and each time the prescription is refilled.

Importance of informing patients of potential risk of serotonin syndrome and neuroleptic malignant syndrome (NMS)-like reactions, particularly with concurrent use of desvenlafaxine and 5-HT_1 receptor agonists (also called triptans), tramadol, tryptophan, other serotonergic agents, or antipsychotic agents. Importance of immediately contacting clinician if signs and symptoms of these syndromes develop (e.g., restlessness, hallucinations, loss of coordination, fast heart beat, increased body temperature, muscle stiffness, increased blood pressure, diarrhea, coma, nausea, vomiting, confusion).

Importance of advising patients not to concurrently take other products containing desvenlafaxine or venlafaxine.

Importance of instructing patients not to take desvenlafaxine with a monoamine oxidase (MAO) inhibitor or within 14 days of stopping the drug, and to allow 7 days after stopping desvenlafaxine before starting therapy with an MAO inhibitor.

Importance of advising patients that they should have regular monitoring of blood pressure while taking desvenlafaxine.

Importance of advising patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) that mydriasis has been reported with desvenlafaxine and that they should be monitored.

Importance of advising patients, their families, and caregivers to observe desvenlafaxine-treated patients for signs of activation of mania/hypomania.

Importance of advising patients that elevations in total cholesterol, LDL, and triglycerides may occur and that measurement of lipid levels may be considered during therapy.

Importance of advising patients to notify their clinician if they develop any allergic signs or symptoms during therapy (e.g., rash, hives, swelling, difficulty breathing).

Risk of cognitive and motor impairment; importance of exercising caution while operating hazardous machinery, including automobile driving, until patients are reasonably certain that desvenlafaxine therapy does not adversely affect their ability to engage in such activities.

Importance of avoiding alcohol during desvenlafaxine therapy.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs or herbal supplements, as well as any concomitant illnesses (e.g., cardiovascular, cerebrovascular, or lipid metabolism disorders; glaucoma) or personal or family history of suicidality or bipolar disorder. Importance of advising patients about the risk of bleeding associated with concomitant use of desvenlafaxine with aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of advising patients that it usually takes several weeks of antidepressant therapy before they will start to feel better. Advise patients not to stop taking the drug if they do not feel the results right away.

Importance of advising patients not to stop taking desvenlafaxine without first talking with their clinician. Importance of patients being aware that discontinuance 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 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.

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

Overview* (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

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

Desvenlafaxine Succinate

Oral		
Tablet, extended-release, film-coated	50 mg (of desvenlafaxine)	**Pristiq**†, Wyeth
	100 mg (of desvenlafaxine)	**Pristiq**†, Wyeth

†Use is not currently included in the labeling approved by the US Food and Drug Administration.

Duloxetine Hydrochloride

■ Duloxetine hydrochloride, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is an antidepressant and anxiolytic agent.

Uses

■ **Major Depressive Disorder** Duloxetine hydrochloride is used for the acute and maintenance treatment of major depressive disorder in adults.

Efficacy of duloxetine for the acute treatment of major depression has principally been established by 4 double-blind, placebo-controlled studies of 8–9 weeks' duration in outpatient settings in adults. In these studies, patients receiving duloxetine (40–120 mg daily) had greater improvements in the 17-item Hamilton depression rating scale (HAMD-17) total score than did patients receiving placebo. No age-, race-, or gender-related differences in efficacy were noted in these studies.

Efficacy of duloxetine for the maintenance treatment of major depressive disorder has been established in a randomized, placebo-controlled relapse prevention study in which 533 adult outpatients who met DSM-IV criteria for major depressive disorder initially received duloxetine 60 mg once daily in a 12-week, open-label acute phase. Patients who responded to treatment during the acute phase were then randomized to continue receiving duloxetine at the same dosage or to receive placebo for 26 weeks in the continuation phase. The duloxetine-treated patients experienced a longer time to relapse of depression compared with the placebo recipients. In addition, more placebo recipients relapsed compared with patients receiving duloxetine (approximately 29% and 17%, respectively).

The manufacturer states that if duloxetine is used for extended periods, the need for continued therapy should be reassessed periodically.

Antidepressant efficacy of duloxetine in hospital settings has not been adequately studied to date.

For further information on treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant for a particular patient, including considerations related to patient tolerance, patient age, and cardiovascular, sedative, and suicidal risk, see Considerations in Choosing Antidepressants under Uses: Major Depressive Disorder, in Fluoxetine Hydrochloride 28:16.04.20.

■ **Generalized Anxiety Disorder** Duloxetine hydrochloride is used for the acute management of generalized anxiety disorder in adults. Efficacy of duloxetine for this indication has been established by 3 placebo-controlled trials of 9–10 weeks' duration in outpatient settings in adults who met DSM-IV criteria for generalized anxiety disorder. In these studies, patients receiving duloxetine (60–120 mg daily) had greater improvements in the Hamilton anxiety scale (HAM-A) total score and the Sheehan Disability Scale (SDS) global functional impairment score than did patients receiving placebo. No age- or gender-related differences in efficacy were noted in these studies.

The manufacturer states that the anxiolytic efficacy of duloxetine for long-term use (i.e., exceeding 10 weeks) has not been established by controlled studies to date. If duloxetine is used for extended periods, the need for continued therapy should be reassessed periodically.

■ **Neuropathic Pain** Duloxetine hydrochloride is used for the management of neuropathic pain associated with diabetic peripheral neuropathy in

adults. Efficacy of duloxetine for this indication has been established by 2 controlled studies of 12 weeks' duration in adults with type 1 or 2 diabetes mellitus and a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for at least 6 months. Patients were excluded from the studies if they met DSM-IV-TR criteria for major depressive disorder and dysthymia. In these studies, 51% of patients receiving duloxetine (60–120 mg daily) and up to 4 g of acetaminophen daily (as needed) reported at least a 30% sustained reduction in pain compared with 31% of those receiving placebo plus acetaminophen (as needed). Some patients in the study experienced a decrease in pain as early as week 1, which persisted throughout the study.

■ **Fibromyalgia** Duloxetine hydrochloride is used for the management of fibromyalgia in adults. Efficacy of duloxetine for this indication has been established by 2 randomized, double-blind, placebo-controlled, fixed-dose studies in adults with a diagnosis of fibromyalgia based on the American College of Rheumatology (ACR) criteria (i.e., history of widespread pain for 3 months and pain present in 11 or more of the 18 specific tender point sites). The first study was of 3 months' duration and enrolled female patients only while the second study was of 6 months' duration and enrolled both male and female patients. Approximately 25% of the patients had concurrent major depressive disorder. Both of these studies compared duloxetine 60 mg once daily or 120 mg daily (given in divided doses in study 1 and as a single daily dose in study 2) with placebo. In addition, Study 2 compared duloxetine 20 mg daily with placebo during the initial 3 months of the 6-month study; after 3 months, the duloxetine dosage was titrated up to 60 mg once daily for the remainder of the study. In these studies, duloxetine therapy in dosages of 60 or 120 mg daily significantly improved the endpoint mean pain scores from baseline and increased the number of patients who had at least a 50% reduction in pain score compared with baseline. Although pain reduction was observed in patients both with and without major depressive disorder, the degree of pain reduction may be greater in patients with major depressive disorder. Some patients experienced a reduction in pain as early as week 1, which persisted throughout the study. Improvement also was noted on measures of function as well as on the Patient Global Impression of Improvement (PGI) scale. Neither study demonstrated an additional therapeutic benefit of 120 mg daily compared with 60 mg daily, and the higher dosage was associated with more frequent adverse effects and early discontinuance of therapy.

The manufacturer states that the efficacy of duloxetine for long-term use (i.e., exceeding 3 months) has not been established by controlled studies to date. However, longer-term efficacy of the drug has been demonstrated for up to 6 months in extension phases of 2 controlled studies to date. The manufacturer recommends that the decision to continue therapy with the drug be based on individual patient response.

■ **Stress Urinary Incontinence** Duloxetine has been used for the management of moderate to severe stress urinary incontinence (SUI)† in women. In a number of placebo-controlled clinical trials involving women with predominantly SUI receiving duloxetine or placebo for up to 12 weeks, duloxetine was significantly better than placebo in reducing the frequency of incontinence episodes (which were reduced by approximately 50% in patients receiving duloxetine) and improving patients' quality of life (as assessed by Incontinence Quality of Life questionnaire scores). Therapy with the drug generally was well tolerated in these studies, with nausea being the most commonly reported adverse effect.

Data from one subsequent analysis suggest that the beneficial effects of duloxetine in women with SUI are maintained for up to 30 months. In addition, some data suggest that combining duloxetine and pelvic floor muscle training exercises may be more effective than either treatment alone. The potential role of duloxetine therapy relative to other forms of treatment (including pelvic floor muscle training, management of fluid intake and voiding, weight loss, devices, and surgery) remains to be established and requires additional study.

Dosage and Administration

■ **Administration** Duloxetine hydrochloride is administered orally without regard to meals. Duloxetine hydrochloride delayed-release capsules should be swallowed whole and should *not* be chewed or crushed, nor should the contents be sprinkled on food or mixed with liquids.

■ **Dosage** Dosage of duloxetine hydrochloride is expressed in terms of duloxetine.

Patients receiving duloxetine should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

The manufacturer recommends that an interval of at least 2 weeks elapse when switching a patient from a monoamine oxidase (MAO) inhibitor to duloxetine. In addition, an interval of at least 5 days should elapse when switching from duloxetine to an MAO inhibitor.

Because withdrawal effects may occur (see Withdrawal Effects under Warnings/Precautions: Other Warnings and Precautions in Cautions), abrupt discontinuance of duloxetine should be avoided. When duloxetine therapy is discontinued, dosage should be tapered gradually and the patient carefully monitored to reduce the risk of withdrawal symptoms. If intolerable symptoms occur following dosage reduction or upon discontinuance of treatment, duloxetine therapy may be reinstituted at the previously prescribed dosage until such symptoms abate. Clinicians may resume dosage reductions at that time but at a more gradual rate.

Major Depressive Disorder For the management of major depressive disorder, the recommended initial dosage of duloxetine in adults is 40 mg daily (given as 20 mg twice daily) to 60 mg daily (given either as 60 mg once daily or 30 mg twice daily). In some patients, it may be desirable to initiate therapy with a dosage of 30 mg once daily given for 1 week, followed by an increase to 60 mg once daily. Although duloxetine dosages of 120 mg daily have been effective, there is no evidence that dosages exceeding 60 mg daily provide additional therapeutic benefit. Safety of dosages exceeding 120 mg daily has not been adequately evaluated.

While the optimum duration of duloxetine therapy has not been established, it generally is agreed that acute depressive episodes require several months or longer of sustained antidepressant therapy. Systematic evaluation of duloxetine has shown that its antidepressant efficacy is maintained for periods of up to 26 weeks in patients receiving 60 mg daily. The manufacturer recommends a maintenance dosage of 60 mg once daily in adults. The manufacturer also recommends that the usefulness of duloxetine be reevaluated periodically in patients receiving long-term therapy.

Generalized Anxiety Disorder For the management of generalized anxiety disorder, the recommended initial adult dosage of duloxetine is 60 mg once daily. In some patients, it may be desirable to initiate therapy with a dosage of 30 mg once daily given for 1 week, followed by an increase to 60 mg once daily. Dosage may be increased in increments of 30 mg once daily (up to a maximum dosage of 120 mg once daily). However, no additional benefit has been demonstrated from duloxetine dosages exceeding 60 mg once daily.

While the optimum duration of duloxetine therapy has not been established, it generally is agreed that generalized anxiety disorder is a chronic condition. The manufacturer states that the efficacy of duloxetine for long-term use (i.e., exceeding 10 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 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. Because progression of diabetic peripheral neuropathy 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.

Fibromyalgia For the management of fibromyalgia, the recommended 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 respond to the initial dosage of 30 mg once daily. Duloxetine dosages exceeding 60 mg daily do not appear to provide 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.

Fibromyalgia is recognized as a chronic condition. The manufacturer states that efficacy of duloxetine in the management of fibromyalgia has been demonstrated in placebo-controlled studies lasting up to 3 months, and that the efficacy of the drug for longer-term use (i.e., exceeding 3 months) has not been established in controlled studies. However, efficacy of the drug has been demonstrated for up to 6 months in extension phases of 2 controlled studies. The manufacturer recommends that the decision to continue therapy with the drug be based on individual patient response.

Stress Urinary Incontinence Although the optimum dosage and duration of duloxetine therapy for the treatment of stress urinary incontinence† in women remain to be established, the most commonly used dosage in controlled trials has been 80 mg daily, usually given as 40 mg twice daily (dosage range: 20–120 mg daily). Some patients may benefit (i.e., reduced risk of nausea and dizziness) from initiating therapy with a duloxetine dosage of 20 mg twice daily for 2 weeks before increasing to the usual dosage of 40 mg twice daily. If adverse effects are bothersome during the first few weeks of therapy at the usual dosage, the dosage may be reduced to 20 mg twice daily. The safety of higher dosages (i.e., 120 mg daily), which have been used in a limited number of women with more severe cases of stress urinary incontinence, requires additional study.

■ **Special Populations** Although there are no specific dosage recommendations for geriatric patients, extra caution is recommended when the duloxetine dosage is increased in elderly patients.

Although the manufacturer makes no specific dosage recommendation for smoking patients, some clinicians recommend a slightly increased duloxetine dosage (by about 15%) in patients who smoke. (See Drug Interactions: Smoking.)

In patients with mild to moderate renal impairment (creatinine clearance 30–80 mL/minute), a lower initial dosage and gradual increase in dosage may be considered. The manufacturer recommends that duloxetine *not* be administered to patients with end-stage renal disease (requiring dialysis), severe renal impairment (creatinine clearance less than 30 mL/minute), or any hepatic insufficiency. (See Specific Populations under Cautions: Warnings/Precautions.)

Treatment of Pregnant Women during the Third Trimester Because some neonates exposed to duloxetine and other selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) or selective serotonin-reuptake inhibitors late in the third trimester of pregnancy have developed severe com-

plications, consideration may be given to cautiously tapering duloxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Pregnancy under Warnings/Precautions: Specific Populations, in Cautions.)

Cautions

■ **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.

Known hypersensitivity to duloxetine or any ingredient in the formulation.

■ **Warnings/Precautions** ***Warnings*** **Worsening of Depression and Suicidality Risk.** 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 (see Pediatric Use under Cautions: Specific Populations) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

Other Warnings and Precautions **Hepatic Effects.** Hepatic failure, sometimes fatal, has been reported in duloxetine-treated patients. The cases presented as hepatitis accompanied by abdominal pain, hepatomegaly, and markedly elevated serum transaminase concentrations (more than 20 times the upper limit of normal) with or without jaundice, reflecting a mixed or hepatocellular pattern of hepatic injury. Duloxetine should be discontinued in any patient who develops jaundice or other evidence of clinically important hepatic dysfunction; therapy should not be resumed unless another cause for the hepatic dysfunction can be established.

Cases of cholestatic jaundice with minimal elevation of serum transaminase concentrations also have been reported. Postmarketing reports indicate that elevated serum transaminase, bilirubin, and alkaline phosphatase concentrations have occurred in duloxetine-treated patients with chronic hepatic disease or cirrhosis.

Duloxetine has been shown to increase the risk of serum transaminase elevations in clinical trials; such elevations resulted in discontinuance 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 to more than 3 times the upper limit of normal occurred in 1.1% of the duloxetine-treated patients compared with 0.2% of those 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, respectively.

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 ordinarily be prescribed to patients with a history of excessive alcohol consumption or evidence of chronic hepatic disease. Patients and clinicians should be aware of the signs and symptoms of hepatic injury (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, unexplained flu-like symptoms), and clinicians should promptly investigate such manifestations in patients receiving the drug.

Orthostatic Hypotension and Syncope. Orthostatic hypotension and syncope 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 dosages exceeding 60 mg daily. Discontinuance 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 reported with selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), including duloxetine, or selective serotonin-reuptake inhibitors (SSRIs), 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., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea).

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

If concurrent therapy with duloxetine and a 5-HT_1 receptor agonist is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when dosage is increased, or when another serotonergic 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 GI bleeding. Bleeding events related to SSRI and SNRI use 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 aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation. (See Drug Interactions: Drugs Affecting Hemostasis.)

Withdrawal Effects. Because withdrawal effects (e.g., dysphoric mood, irritability, agitation, nausea/vomiting, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, nightmares, hypomania, tinnitus, seizures) may occur, abrupt discontinuance of duloxetine should be avoided. (See Dosage and Administration: Dosage.)

If intolerable symptoms occur following dosage reduction or discontinuance, reinstitute previously prescribed dosage until symptoms abate, then resume more gradual dosage reductions.

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 the drug; therefore, use with caution in patients with a history of seizures.

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

Clinically Important Drug Interactions. Because both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism, the potential exists for clinically important drug interactions when duloxetine is concurrently administered with CYP1A2 inhibitors, CYP2D6 inhibitors, and CYP2D6 substrates.

Concurrent therapy with MAO inhibitors used for treatment of depression is contraindicated. (See Serotonin Syndrome 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, duloxetine should not ordinarily be prescribed to patients with a history of excessive alcohol consumption or evidence of chronic hepatic disease. (See Hepatic Effects under Warnings/Precautions: Other Warnings and Precautions, in Cautions and also see Drug Interactions: Alcohol.)

Potential pharmacologic interaction when duloxetine is given with or substituted for other centrally acting drugs, including those with a similar mechanism of action; CNS-active drugs should be used with caution in patients receiving duloxetine.

Hyponatremia/Syndrome of Inappropriate Antidiuretic Hormone Secretion. Treatment with SSRIs and SNRIs, including duloxetine, may result in hyponatremia. In many cases, hyponatremia 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 hyponatremia appeared reversible when duloxetine was discontinued. Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be at greater risk of developing hyponatremia. Signs and symptoms 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, syncope, seizures, coma, respiratory arrest, and death. Initiate appropriate medical intervention and consider drug discontinuance in patients with symptomatic hyponatremia.

Concomitant Illnesses. Experience with duloxetine in patients with concomitant diseases is limited. (See Hepatic Impairment and see Renal Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

Because alterations in gastric motility may affect the stability of the enteric coating of the pellets contained in duloxetine capsules, the drug should be used with caution in patients with conditions that may slow gastric emptying (e.g., in some patients with diabetes mellitus).

Duloxetine has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease; such patients were generally excluded from clinical studies. The manufacturer states that duloxetine use was not associated with the development of clinically important ECG abnormalities in controlled clinical studies of up to 13 weeks' duration.

Duloxetine worsens glycemic control in some patients with diabetes. In the 12-week acute treatment phase of 3 clinical studies in patients with diabetic peripheral neuropathy, small increases in fasting blood glucose were observed in the duloxetine-treated patients compared with those receiving placebo. In the extension phase of these studies, which lasted up to 52 weeks, fasting blood glucose increased by 12 mg/dL in the duloxetine-treated patients and decreased by 11.5 mg/dL in the routine care group; increases in glycosylated hemoglobin (hemoglobin A_{1c}) were observed in both groups of patients although the average increase was 0.3% greater in the duloxetine-treated patients compared with those receiving routine care.

Controlled Narrow-Angle Glaucoma. Possible increased risk of mydriasis; use with caution in patients with *controlled* narrow-angle glaucoma. Contraindicated in patients with such glaucoma that is not controlled.

Urinary Hesitation and Retention. Duloxetine belongs to a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during therapy, consider possibility that they may be drug-related. (See Uses: Stress Urinary Incontinence.)

Cases of urinary retention have been reported during postmarketing experience; in some of these cases, hospitalization and/or catheterization has been necessary.

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Some neonates exposed to selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) or selective serotonin-reuptake inhibitors late in the third trimester of pregnancy have developed complications that have sometimes been severe and required prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care in special-care nurseries. Such complications can arise immediately upon delivery and usually last several days or up to 2–4 weeks. Clinical findings reported to date in the neonates have included respiratory distress, cyanosis, apnea, seizures, temperature instability or fever, feeding difficulty, dehydration, excessive weight loss, vomiting, hypoglycemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, reduced or lack of reaction to pain stimuli, and constant crying. These clinical features appear to be consistent with either a direct toxic effect of the SNRI or selective serotonin-reuptake inhibitor or, possibly, a drug withdrawal syndrome. It should be noted that, in some cases, the clinical picture was consistent with serotonin syndrome (see Drug Interactions: Drugs Associated with Serotonin Syndrome, in Fluoxetine Hydrochloride 28:16.04.20). When treating a pregnant woman with duloxetine during the third trimester of pregnancy, the clinician should carefully consider the potential risks and benefits of such therapy. Consideration may be given to cautiously tapering duloxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Treatment of Pregnant Women during the Third Trimester under Dosage and Administration: Special Populations.)

Lactation. Duloxetine is distributed into human milk. At steady state, concentrations in breast milk are approximately one-fourth the maternal plasma concentrations. Because the safety of duloxetine in infants is not known, use in nursing women is not recommended. However, if the clinician determines that the potential benefits of duloxetine therapy for the mother outweigh the potential risks to the infant, dosage adjustment is not required since lactation does not affect pharmacokinetics.

Pediatric Use. Safety and efficacy of duloxetine in children younger than 18 years of age have not been established.

FDA warns that a greater risk of suicidal thinking or behavior (suicidality) occurred during first few months of antidepressant treatment (4%) compared with placebo (2%) in children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders based on pooled analyses of 24 short-term, placebo-controlled trials of 9 antidepressant drugs (selective serotonin-reuptake inhibitors [SSRIs] and other antidepressants). However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

Carefully consider these findings when assessing potential benefits and risks of duloxetine in a child or adolescent for any clinical use. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Geriatric Use. Approximately 5.9, 33, and 7.9% of patients studied in clinical trials of duloxetine for major depressive disorder, diabetic peripheral neuropathy, and fibromyalgia, respectively, were 65 years of age or older. The generalized anxiety disorder clinical trials did not include sufficient numbers of patients 65 years of age or older to determine whether they respond differently than younger adults. Although no overall differences in efficacy or safety were observed between geriatric and younger patients in the major depressive disorder, diabetic peripheral neuropathic pain, and fibromyalgia clinical trials and other clinical experience has not revealed any evidence of age-related differences, the possibility that some older patients may exhibit increased sensitivity to the drug cannot be ruled out.

Clinically important hyponatremia has been reported in geriatric patients, who may be at greater risk for this adverse effect. (See Hyponatremia/Syndrome of Inappropriate Antidiuretic Hormone Secretion under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

Hepatic Impairment. Substantially increased exposure to duloxetine; use is not recommended in patients with hepatic insufficiency or with substantial alcohol use. (See Hepatic Effects under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

Renal Impairment. Increased plasma concentrations of duloxetine and its metabolites; use is not recommended in patients with end-stage renal disease (requiring dialysis) or severe renal impairment (creatinine clearance less than 30 mL/minute).

Population pharmacokinetic analyses suggest that mild to moderate renal impairment has no clinically important effect on duloxetine apparent clearance.

■ **Common Adverse Effects** Adverse effects reported in 5% or more of patients with major depressive disorder receiving duloxetine and at an incidence at least twice that reported with placebo include nausea, dry mouth, constipation, decreased appetite, fatigue, somnolence, and increased sweating.

Adverse effects reported in 5% or more of patients with generalized anxiety disorder receiving duloxetine and at an incidence at least twice that reported with placebo include nausea, fatigue, dry mouth, somnolence, constipation, insomnia, decreased appetite, vomiting, hyperhidrosis, decreased libido, delayed ejaculation, and erectile dysfunction.

Adverse effects reported in 5% or more of patients with diabetic peripheral neuropathy receiving duloxetine and at an incidence at least twice that reported with placebo include nausea, somnolence, dizziness, dry mouth, constipation, hyperhidrosis, decreased appetite, and asthenia.

Adverse effects reported in 5% or more of patients with fibromyalgia receiving duloxetine and at an incidence at least twice that reported with placebo include nausea, dry mouth, constipation, decreased appetite, somnolence, agitation, and hyperhidrosis.

Drug Interactions

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Substrates of cytochrome P-450 (CYP) 2D6 isoenzyme (e.g., tricyclic antidepressants [TCAs; amitriptyline, desipramine, imipramine, nortriptyline], phenothiazines, class IC antiarrhythmics [flecainide, propafenone]): potential pharmacokinetic (increased AUC of the substrate) interactions. Use with caution. Consider monitoring plasma TCA concentrations and reducing the TCA dosage if a TCA is administered concurrently with duloxetine.

Substrates of CYP1A2, CYP3A, CYP2C9, or CYP2C19 isoenzymes: clinically important pharmacokinetic interaction generally is considered unlikely.

■ **Drugs Affecting Hepatic Microsomal Enzymes** Potent inhibitors of CYP1A2 (e.g., fluvoxamine, some quinolone anti-infective agents [e.g., ciprofloxacin, enoxacin]): potential pharmacokinetic (increased plasma duloxetine concentrations) interaction. Avoid concomitant use.

Potent inhibitors of CYP2D6 (e.g., fluoxetine, paroxetine, quinidine) isoenzymes: potential pharmacokinetic interaction (increased plasma duloxetine concentrations).

Concomitant administration of duloxetine and fluvoxamine, a potent CYP1A2 inhibitor, in poor CYP2D6 metabolizers resulted in a sixfold increase in duloxetine area under the plasma concentration-time curve (AUC) and peak plasma concentrations.

■ **Drugs Affecting Hemostasis** Altered anticoagulant effects, including increased bleeding, have been reported when selective serotonin-reuptake inhibitors (SSRIs) or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), including duloxetine, were concurrently administered with warfarin or other anticoagulants. The manufacturer recommends carefully monitoring patients receiving warfarin during initiation and discontinuance of duloxetine therapy.

Potential pharmacologic (increased risk of bleeding) interaction with aspirin or other nonsteroidal anti-inflammatory agents; use with caution.

■ **Drugs that Affect Gastric Acidity** Theoretical risk of altered duloxetine bioavailability if administered with drugs that increase gastric pH. However, no clinically important effect was demonstrated when duloxetine was administered with aluminum- and magnesium-containing antacids or famotidine.

Whether the concomitant administration of proton-pump inhibitors affects duloxetine absorption is currently unknown.

■ **Alcohol** Potential pharmacologic (increased risk of hepatotoxicity) interaction; avoid concomitant use in patients with substantial alcohol use. (See Hepatic Effects under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

Duloxetine has not been shown to potentiate the impairment of mental and motor skills caused by alcohol.

■ **Antihypertensive Agents** Potential pharmacologic (increased risk of hypotension and syncope) interaction.

■ **Benzodiazepines** Lorazepam does not appear to affect the pharmacokinetics of duloxetine.

Temazepam does not appear to affect the pharmacokinetics of duloxetine.

■ **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$_1$ Receptor Agonists ("Triptans")** Pharmacologic interaction (potentially life-threatening serotonin syndrome) if used concurrently with 5-HT$_1$ reeeptor agonists (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan). If concomitant use is clinically warranted, the patient should be observed carefully, particularly during treatment initiation, when dosage is increased, or when another serotonergic agent is initiated. (See Serotonin Syndrome under Warnings/Precautions:Other Warnings and Precautions, in Cautions.)

■ **Monoamine Oxidase (MAO) Inhibitors** Pharmacologic interaction (potentially fatal serotonin syndrome); concomitant use is contraindicated. The manufacturer recommends that at least 2 weeks should 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 Norepinephrine-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.)

Concomitant administration of duloxetine and fluvoxamine, a potent CYP1A2 inhibitor, in poor CYP2D6 metabolizers resulted in a six-fold increase in duloxetine AUCs and peak plasma concentrations.

■ **Serotonergic Drugs** Potential pharmacologic interaction (potentially life-threatening serotonin syndrome) with drugs affecting serotonergic neurotransmission, including linezolid (an anti-infective agent that is a nonselective, reversible MAO inhibitor), lithium, tramadol, and St. John's wort (*Hypericum perforatum*); 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 dosage adjustment is not necessary. However, some clinicians recommend 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 concomitant administration.

■ **Thioridazine** Potential pharmacokinetic (increased plasma thioridazine concentrations) interaction with resulting increased risk of serious ventricular arrhythmias and sudden death; concomitant use is not recommended by manufacturer of duloxetine.

Description

Duloxetine hydrochloride, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is an antidepressant and anxiolytic agent. The drug also 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.

The exact mechanisms of the antidepressant, anxiolytic, and central pain inhibitory actions of duloxetine have not been fully elucidated, but appear to be associated with the drug's potentiation of serotonergic and noradrenergic activity in the CNS. Like venlafaxine and desvenlafaxine, duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine does not inhibit monoamine oxidase (MAO) and has not demonstrated significant affinity for dopaminergic, adrenergic, cholinergic, γ-aminobutyric acid (GABA), glutamate, histaminergic, and opiate receptors in vitro.

Although the precise mechanism of action of duloxetine in stress urinary incontinence is unknown, it is thought to be related to potentiation of serotonin and norepinephrine activity in the sacral spinal cord, which increases urethral closure forces and thereby reduces involuntary urine loss.

Duloxetine is extensively metabolized in the liver, principally via oxidation by the cytochrome P-450 (CYP) 2D6 and 1A2 isoenzymes. 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.

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.

Importance of promptly reporting any manifestations of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, unexplained flu-like symptoms) to clinician.

Importance of informing patient of risk of severe liver injury associated with concomitant use of duloxetine and heavy alcohol intake. (See Hepatic Effects under Warnings/Precautions: Other Warnings and Precautions and also see Drug Interactions: Alcohol.)

Risk of psychomotor impairment; importance of exercising caution while operating hazardous machinery, including automobile driving, until patient gains experience with the drug's effects.

Importance of advising patients of risk of orthostatic hypotension and syncope, particularly during initial therapy and subsequent dosage escalation and during concomitant therapy with drugs that may potentiate the orthostatic effect of duloxetine.

Importance of informing patients of risk of serotonin syndrome with concurrent use of duloxetine and 5-HT$_1$ receptor agonists (also called triptans), tramadol, or other serotonergic agents. Importance of seeking immediate medical attention if symptoms of serotonin syndrome develop.

Importance of taking medication exactly as prescribed by the clinician. Importance of informing patients that the delayed-release capsules should be swallowed whole and should not be chewed or crushed, nor should the capsule contents be sprinkled on food or mixed with liquids.

Importance of continuing duloxetine therapy even if a response is not evident within 1–4 weeks, unless directed otherwise.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., bipolar disorder, liver disease) or family history of suicidality or bipolar disorder. Risk of bleeding associated with concomitant use of duloxetine with aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation.

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

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

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**

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Venlafaxine Hydrochloride

■ Venlafaxine hydrochloride, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is a phenylethylamine-derivative antidepressant and anxiolytic agent.

Uses

■ **Major Depressive Disorder** Venlafaxine hydrochloride is used in the treatment of major depressive disorder. Efficacy of venlafaxine conventional tablets for the management of major depression has been established in several placebo-controlled studies in outpatient settings in patients who had major depression and in 1 placebo-controlled study in a hospital setting in patients who had major depression with melancholia. Efficacy of venlafaxine extended-release capsules for the treatment of major depression also has been established by controlled studies of 8–12 weeks' duration in outpatient settings; however, the safety and efficacy of venlafaxine extended-release capsules in hospitalized patients with major depression have not been adequately evaluated.

In 4 studies of 6 weeks' duration in adult outpatients with major depression, venlafaxine in dosages of 75–225 mg daily administered in 2 or 3 divided doses as conventional tablets was found to be superior to placebo on at least 2 of the following 3 clinical measures of depression: Hamilton Depression Rating Scale (HAM-D) total score, HAM-D depressed mood item, and the Clinical Global