CONCERTA® (methylphenidate hydrochloride) Extended-release Tablets

Briefing Document

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1 EXECUTIVE SUMMARY

Attention-Deficit/Hyperactivity Disorder (ADHD) was characterized as a medical disorder more than 100 years ago. It is a neurophysiologic disorder that presents with a pattern of behavioral disturbances that have a significant impact on the social functioning, academic performance, and self-esteem of the affected child. Although the molecular genetics of this disorder have not been elucidated completely, there is strong evidence from twin studies that ADHD is inheritable and that up to 80% of the variance in ADHD can be explained by a genetic etiology. The prevalence of ADHD has been estimated to be as high as 10% of all school-aged children, with boys being affected 3 times more often than girls. The prevalence of ADHD in the United States parallels the prevalence worldwide.

ADHD is diagnosed by a set of well-defined and validated clinical criteria. While ADHD can manifest as a sole diagnosis, comorbid conditions are present in up to 50% of the affected individuals and can significantly affect diagnosis, therapy, and outcomes, including the risk of suicide and suicidal behavior. Among the most common comorbidities are: learning disorders, oppositional-defiant disorder, conduct disorder, depression, and anxiety disorder. The presence of comorbidities can be expected to confound the evaluation of undesirable behaviors, which may be attributed to either adverse events or to the unmasking of previously undiagnosed psychiatric conditions.

The diagnosis of ADHD, especially untreated ADHD, is associated with a considerable effect on health-related quality of life (HRQoL) and societal functioning. Children with untreated ADHD are more likely to have poor self-esteem, academic underachievement, poor peer relationships, and increased parental stress. In 30% to 60% of children with ADHD, the condition is believed to persist in adulthood. Adults with untreated

ADHD are more likely to have lower occupational functioning and increased risk of motor vehicle violations, accidents, and substance use disorders.

Recent efforts by advocacy groups, professional societies, and the US Department of Education have led to increased awareness and identification of the disorder.

ADHD has received the attention of the professional and public media in recent times, with particular emphasis on the rising prevalence of ADHD and the increasing use of stimulant medications in the United States. There has been much debate surrounding the cost of ADHD to society, in terms of both the cost of treating ADHD and the cost of untreated ADHD. Well-studied and proven treatment options for ADHD include pharmacotherapy and behavioral therapy. The National Institutes of Mental Health-sponsored Multimodal Treatment Study of Children With ADHD (MTA Study) conclusively demonstrated that well-monitored methylphenidate treatment alone or in combination with behavioral therapy was superior to behavioral therapy alone over 14 months.

Methylphenidate is a schedule II drug, initially approved by the US FDA in 1955 for the treatment of the symptoms of ADHD. The efficacy of methylphenidate in the treatment of ADHD is well established. During the June 2005 Pediatric Advisory Committee meeting, the FDA presented postmarketing adverse event reports regarding cardiovascular and psychiatric adverse events seen in the pediatric population using stimulant medications.

For the most serious cardiovascular adverse events reported by the FDA, the estimated reporting rate of non-excluded deaths (deaths that could not be specifically attributed to a cause) was 0.27 per 100,000 patient-years of treatment with methylphenidate. The rate of sudden cardiac death was estimated to be 0.19 per 100,000 patient-years with methylphenidate. The rate of serious non-fatal cardiovascular events was estimated to be 0.22 per 100,000 patient-years with methylphenidate. The background rate for sudden

cardiac death in children and young adults is approximately 1.3 to 8.5 per 100,000 persons. Even with a many-fold correction for under-reporting in the passive surveillance system, the observed rate of sudden deaths in patients receiving methylphenidate is consistent with the background rate.

Suicidal ideation was reported in the FDA's June 2005 CONCERTA postmarketing safety review. These reports are confounded because of the high frequency of comorbid conditions in patients with ADHD and the prevalence of suicidal behaviors in the general adolescent population. Based on these CONCERTA® spontaneous reports, the estimated rate of suicidal ideation was calculated to be 0.65 cases per 100,000 patient-years. Even with a many-fold correction for under-reporting in the passive surveillance system, the observed rate of suicidal ideation is lower than the background rate in children.

It is customary to balance the therapeutic benefits and potential risks a patient is exposed to during treatment. Untreated ADHD is associated with severe consequences. Clinical trials have shown that methylphenidate is effective in improving the symptoms of the disorder in children, adolescents, and adults. Benefits to patients are numerous and have a significant positive impact on the patient's quality of life (QOL). As no pharmacologic treatment is without risk, patients who are receiving methylphenidate may be exposed to some increased risk of adverse events. Although cognizant of the beneficial effects of methylphenidate, the FDA has recently highlighted concerns regarding serious cardiovascular and psychiatric adverse events reported with ADHD medications. In January 2006, FDA requested that all stimulant products include an additional warning regarding the possibility of sudden death in patients with structural cardiac abnormalities.

The current labeling for CONCERTA contains clear contraindications and warnings related to cardiovascular and psychiatric adverse events reported with the use of methylphenidate.

While much of the literature intended to discredit ADHD and its treatment is polemical and alarmist in nature, genuine attempts to untangle the controversies surrounding this disorder have been and continue to be made.

2 ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD)

2.1 ADHD Mainly Affects Young Children and Adolescents

ADHD is the most common psychiatric disorder of childhood.[1] It is a neurophysiologic disorder that presents as a persistent pattern of inattention and/or hyperactivity/impulsivity that is more severe than observed in individuals of a comparable developmental stage. ADHD is associated with significant morbidity in the areas of social functioning, academic performance, and self-esteem. Often, children with ADHD are unable to behave appropriately or function in social or group settings, are unable to infer emotion or intent from facial expressions or vocal clues, are unpopular with peers, and have difficulty in establishing and maintaining enduring relationships.[2] These children are also more likely to sustain severe injuries if their ADHD is untreated and are at a higher risk of developing substance use disorders as adults.[3] ADHD also exacts a price on the family, as evidenced by increased parental or caregiver stress.[4-6]

It is difficult to design robust epidemiologic studies of ADHD; as a result, prevalence estimates of ADHD are sensitive to study methodology and have varied between 2% and 18%.[7] ADHD is estimated to affect anywhere from 1% to 10% of school-aged children.[8-13] Analysis of the 2003 National Survey of Children's Health conducted by the Centers for Disease Control[14] yielded an estimate of approximately 4.4 million children reported to have a history consistent with a diagnosis of ADHD; of these approximately 2.5 million were noted to be taking medication for this disorder. The national prevalence for this disorder was estimated to be 7.8%, with the disorder being reported 3 times more frequently among male children than female children. The prevalence of reported ADHD increased with age, and the greatest prevalence (14.9%) was noted among 16-year-old males. ADHD diagnosis was

reported significantly more often in families with incomes below the poverty threshold. The prevalence of ADHD among girls appears to be increasing as well.[15] Data from the US National Ambulatory Medical Healthcare Survey revealed a 2.7-fold increase in office visits for ADHD among girls over the time interval between 1991-1992 and 1997-1998. Another epidemiologic study of ADHD in children suggests that its prevalence may be 2 to 3 times higher than the figure of 3% to 5% that is most often cited, although there are data that support both under-diagnosis and over-diagnosis.[16]

A systematic computerized review of the literature on ADHD in Brazil was conducted, and the findings were compared to those from studies in developed countries[17]. Using criteria defined by the year 2000 Diagnostic & Statistical Manual for Mental Disorders, 4th Edition (DSM-IV-TR), the prevalence rate of ADHD was found to be 5.8%. Based on the pattern of ADHD comorbidity in clinical samples, the family genetic data suggested a 39% family transmission in clinical samples and a role of some potential candidate genes in dopaminergic and noradrenergic systems. The data on the efficacy of methylphenidate in the disorder were very similar to findings from other countries; taken together, these findings support that ADHD is not a cultural construct but a true biologic disease.

2.2 ADHD Is an Inheritable Disorder

Although ADHD is a clinically heterogeneous disorder of inattention, hyperactivity, and impulsivity, there is strong evidence that ADHD is a heritable disorder.[18, 19] Family studies consistently support the assertion that ADHD runs in families. Several studies of twins have demonstrated that up to 80% of the etiology in ADHD can be attributable to genetic factors.[20, 21] Although ADHD has been extensively studied, relatively little is known about the biologic basis of ADHD. Gene association studies have focused on dopaminergic

genes and genes associated with other neurotransmitter systems.[22] Certain alleles of the genes coding for the dopamine D4 receptor and the dopamine transporter occur more frequently in children with ADHD than in healthy controls, and a major challenge is to clarify how genetic susceptibility is translated into the disorder.[23] A meta-analysis of recent literature shows statistically significant evidence of the association of ADHD with 7 genes: DRD4, DRD5, DAT, DBH, 5-HTT, HTR1B, and SNAP-25.[24]

2.3 Diagnosis and Treatment of ADHD Is Often Complicated by the Presence of Other Psychiatric and Neurologic Disorders

Children with ADHD often have comorbid conditions that make the diagnosis and treatment of ADHD especially challenging.[25] In fact, comorbidity appears to be the norm rather than the exception for children with ADHD.[26] Accurate differential diagnostic assessment is essential to providing adequate therapy and assessing the outcomes of therapy. The presence of comorbidities can also be expected to confound the evaluation of undesirable behaviors, which may be attributed to either adverse events or to the unmasking of previously undiagnosed psychiatric conditions.

The most common comorbid conditions are oppositional defiant disorder (ODD) and conduct disorder (CD), with a prevalence rate of approximately 25% to 40% among children with ADHD[27], followed by learning disabilities with a prevalence of approximately 20% to 25%.[28] Approximately 27% of the children diagnosed with ADHD may also have anxiety disorder or depressive disorder.[29] Other diagnoses known to coexist with ADHD include bipolar syndrome and Tourette's syndrome.[30]

The National Institutes of Mental Health and Department of Education-sponsored MTA Study included a substantial number of children with comorbid disorders.[31] Children

with ADHD and anxiety disorder were equally likely to respond to either medication or behavioral therapy, children with ADHD and ODD or CD responded best to MTA medication therapy, while children with multiple comorbid disorders responded optimally to combined MTA behavioral and medication therapy.

In an elementary school-based prevention of CD program, 7,231 first- through fourth-grade children were screened for cross-setting disruptive behavior[32]; ADHD and ODD were the most frequent diagnoses. Mood and anxiety disorders were infrequent as single diagnoses. Patterns of comorbidity demonstrated that both externalizing and internalizing disorders commonly co-occurred with ADHD. More severe degrees of psychopathology and psychosocial risk were noted in the subgroup of youths with ADHD plus a comorbid externalizing disorder.

Relatively little is known about the comorbidity between ADHD and tic disorders. In a 4-year study of 128 male children and adolescents with ADHD and 110 male controls, subjects with ADHD showed more tic disorders at baseline, and more new onsets were reported at follow-up. ADHD and tic disorders appeared to be independent in course: in contrast to low rates of ADHD remission, tic disorders mostly remitted.[33]

A recent population-based case-control study of all newly diagnosed unprovoked seizures among Icelandic children younger than 16 years of age addressed the question of whether ADHD is associated with increased risk of seizures.[34] A history of ADHD was 2.5-fold more common among children with newly diagnosed seizures than among control subjects. The association was restricted to ADHD predominantly inattentive type, not ADHD predominantly hyperactive-impulsive type or ADHD combined type. This association has the potential to confound the evaluation of seizure activity in children after initiation of stimulants.

2.4 ADHD Has a Significant Effect on Quality of Life and Functioning

ADHD imparts profound detrimental results on virtually all aspects of a patient's QOL. Children with ADHD are at greater risk for severe, long-term, negative outcomes such as lower educational and employment attainment.[35] Young people with ADHD are at increased risk of academic failure, dropping out of school or college, teenage pregnancy, family conflicts, social ostracism, and criminal behavior.[36, 37] Individuals with ADHD report increased feelings of anxiety and depression, as well as diminished self-esteem, as a result of their symptoms and consequences.[13]

A growing body of evidence suggests that symptoms of ADHD persist into adulthood and are associated with ongoing impairment and comorbidity. Although adolescence frequently coincides with a reduction in symptoms of over-activity, symptoms of inattention, impulsiveness, and restlessness remain and often result in academic, behavioral, and social impairment. Recent studies suggest that 30% to 60% of affected children will continue to show significant symptoms of the disorder into young adulthood.[38]

As a direct result of associated symptoms, children and adolescents with ADHD are particularly vulnerable to accidental injuries, driving impairment, substance abuse, academic failure, and strained peer relationships. ADHD also results in increased stress and conflict in the family setting and significant compromise of a patient's HRQoL.

2.4.1 Effect of ADHD and ADHD Treatment on Accidental Injury

Children and adolescents with ADHD are at a higher risk of accidental injury attributable to their tendency towards impulsive, overactive behavior.[39, 40] When compared with children without ADHD, children with ADHD who become injured are more likely to

sustain severe injuries, including lacerations, fractures, and sprains,[37, 41, 42] and to make more frequent emergency department (ED) visits.[43]

Data from multiple studies indicate that extended stimulant treatment is associated with decreased ED visits because treatment effectively reduces the symptoms of ADHD, including inattention and hyperactivity, which may also reduce the likelihood of accidents. A review of complete school and medical records of a cohort of 313 school children identified that those children with ADHD on stimulant treatment (n = 231) had lower mean and median values for ED visits compared to those with ADHD not on stimulants (n = 82) and that the annual rate of ED visits declined with increasing proportion of time on stimulants.[44]

2.4.2 Effect of ADHD and ADHD Treatment on Driving Errors

Adolescents and adults with ADHD have a higher risk of adverse driving outcomes. According to the National Highway Traffic Safety Administration, automobile accidents are more common among those with ADHD and may be associated with a higher rate of fatality.[45] Multiple studies have demonstrated that adolescents and young adults with ADHD were 2 to 4 times more likely to be involved in a traffic accident, 4 times more likely to be at fault in the accident, and 3 times more likely to incur associated injuries as a result of the accident.[44, 46-48] Young drivers with ADHD were also more likely to engage in risky driving behaviors.

Studies have demonstrated that treatment with methylphenidate has improved driving performance in young adults with ADHD in both simulator and on-road driving tests.[47, 49-51] Compared with placebo, methylphenidate helped to reduce inattentive driving errors (ie, distracted, missed turns, failed to see signal and ran a red light or stop sign, drove off road) and reduce driving safety risks in subjects with ADHD.[52]

2.4.3 Effect of ADHD and ADHD Treatment on Substance Use Disorder

Evidence indicates that ADHD patients who have not been treated for their symptoms are at a heightened risk for developing substance use disorders (SUDs) compared with the general population (52% versus 27%, respectively).[3, 53] Moreover, untreated ADHD is associated with an earlier onset of psychoactive SUDs, with substance abuse beginning approximately 3 years earlier in patients with ADHD than in patients without ADHD.[3] In addition, patients with ADHD have an increased propensity for SUDs, putting them at greater risk for developing serious health complications associated with SUDs, including infectious diseases such as hepatitis, tuberculosis, and acquired immunodeficiency syndrome.[54]

A recent meta-analysis reported reduced risks for later drug and alcohol use disorders in patients receiving stimulant therapy during childhood who were followed into adolescence.[55] Four of the 6 studies analyzed showed striking protective effects of early stimulant treatment. A longitudinal study revealed that boys with ADHD are more likely to develop SUDs than boys without ADHD, and this potential increased risk was reduced by 85% in boys with ADHD who were receiving pharmacotherapy.[56] A large, prospective, longitudinal, population-based study also indicated that psychostimulant treatment (85% of patients treated with methylphenidate) was associated with a significant and clinically meaningful decrease in alcohol and drug abuse among children with a childhood diagnosis of ADHD.[57] This decrease was observed even among those whose parents were substance abusers. These studies demonstrate that treating ADHD with methylphenidate does not make these patients more susceptible for SUDs due to sensitization and, in fact, may be protective.[58]

2.4.4 Effect of ADHD and ADHD Treatment on Academic Performance

Children with ADHD may experience academic difficulties, likely because of multiple factors that include inattention, poor organizational and study skills, poor working memory, and cognitive deficits.[59] Children diagnosed with ADHD tend to have more suspensions, poorer achievement, more off-task behavior, higher rates of fidgeting and out-of-seat behavior, and less productivity overall.[60] Both retrospective and prospective controlled studies have shown that adolescents and adults previously diagnosed with ADHD had significantly lower academic performances, along with poorer social, emotional, and adaptive functioning.[61] In general, these individuals completed significantly less formal schooling (about 2 years less, on average) and had lower-ranking occupational positions than those without ADHD.[35] Adult limitations because of behavioral manifestations are likely compounded by academic difficulties experienced as children with ADHD.

Treatment with stimulant medications has been shown to improve ADHD symptoms in the academic environment and may contribute to decreased academic failure. Notable behavioral improvements induced by stimulant medication include decreased interrupting, fidgeting, and finger tapping, as well as increased on-task behavior.[62] In a study of children with ADHD and tic disorder, those who received 3 doses of methylphenidate twice daily for 2 weeks showed marked behavioral improvement during structured classroom academic activities, with decreased levels of negative behaviors in the lunchroom and on the playground compared with those who received placebo.[63] In a comparison, open-label study of Taiwanese children diagnosed with ADHD, 68% to 78% of children showed improvement in their behavior in the classroom and at home, and 61% to 66% showed improvement in academic learning of Chinese and arithmetic after treatment with methylphenidate.[64]

In a large, double-blind, cross-over study of 3 doses of methylphenidate in adolescents clinically diagnosed with ADHD, beneficial effects were seen across the ecologically valid measures of classroom performance such as note-taking, quiz performance, written language, and study hall assignments.[60] Similar results were also seen in a within subject, balanced-placebo design study of boys diagnosed with ADHD who were studied in a summer treatment program and in the regular classroom setting.[65] These study results added to the existing evidence that stimulant medication is an effective treatment for children with ADHD in a variety of domains or impairment: parent and peer interactions, classroom behavior, and class work.

2.4.5 Effect of ADHD and ADHD Treatment on Family and Peer Relationships

ADHD results in a significant detriment to a patient's relationships with parents, caregivers, siblings, and peers. Impulsivity and difficulty following rules—core symptoms for this disorder—may result in oppositional behavior or problems with conduct. Children with ADHD have also been noted to be intrusive in their social interactions. These behaviors frequently result in peer rejection.[66, 67]

Within a family, the presence of a child with ADHD results in increased likelihood of disturbances in family and marital functioning, disrupted parent-child relationships, and increased levels of parental stress, particularly when ADHD is comorbid with other conduct problems.[4-6] Disruption caused by symptoms and behavioral manifestations is a significant problem facing siblings of children with ADHD, as well.[68] These siblings reported increased feelings of victimization through aggressive acts from their ADHD siblings, increased responsibilities of care-taking, and increased feelings of sorrow.

In addition to the profound effects that ADHD can induce in familial relationships, children with ADHD report significant impairment in peer relationships. Adolescents with ADHD may be excluded from social networks with more social peers and thus choose friends who are more involved in problem behaviors.[69] In one study, children with ADHD were lower on social preference, higher on social impact, less well-liked, and more often in the rejected social status category when ranked by classmates. They also reported fewer friends.[70]

Adults with ADHD are more likely to experience interpersonal difficulties with employers and colleagues. Lateness, absenteeism, excessive errors, and an inability to complete work responsibilities often plague adults with ADHD.[71] Relationship difficulties are reported more frequently, and the risk of drug and substance abuse is significantly increased in adults with persisting ADHD symptoms who have not been receiving medication.[72]

Treatment with stimulant drugs has resulted in improved parent-child interactions, increased on-task behavior, and improved compliance both at home and in social settings.[62] In the latter, stimulant treatment resulted in improvements in peer-nomination rankings and increased attention span during sports activities.[62]

2.4.6 Effect of ADHD and ADHD Treatment on Health-Related Quality of Life

Health-related QOL is one aspect of patients' lives that is strongly affected by ADHD but difficult to measure. Traditionally, ADHD treatment and characterization has focused on symptom evaluation; however, a more robust consideration should include the effects on other HRQoL aspects as well. In one study, ADHD children with physical health scores comparable to healthy children scored lower in HRQoL in all psychosocial domains.[73] Decreased HRQoL scores were positively correlated with symptom severity and the presence of multiple comorbidities. Such analysis evaluating HRQoL, using validated

questionnaires, confirmed the extent of relationship problems experienced by individuals with ADHD, including behavioral problems, emotional-behavioral functions, mental health, and self-esteem. Although difficult to quantify, these effects represent significant detriments to patients' lives.

3 DIAGNOSIS OF ADHD

3.1 Presentation of ADHD Varies by Age and Sex of the Child

There is developmental variability in the presentation of ADHD. The prevalence of ADHD is estimated at 3% to 7% of children. Boys are more often affected than girls; the ratio ranges according to the population studied, from 9:1 to 2.5:1. However, increasingly, cases involving girls are being identified.[30] The symptom of impulsivity displayed by young children with ADHD may decrease over time, whereas inattention may persist even into adulthood.[74-77] Furthermore, the hyperactivity associated with ADHD in children often develops into a sense of inner restlessness in adolescents and adults, accompanied by characteristics such as poor concentration, daydreaming, and forgetfulness.[78]

A study of gender influences on ADHD in youths found that, although girls and boys were at the same relative risk for various comorbid outcomes, the clinical presentation differed.[79] This finding may reflect the fact that girls typically do not disrupt class even though they may present with clinically meaningful levels of inattention. As disruptive behavior is typically a reason for referral and evaluation for the presence of ADHD, girls with ADHD may be under-identified and under-treated.[18]

3.2 ADHD Is Diagnosed Using Well-Defined Criteria

The year 2000 Diagnostic & Statistical Manual for Mental Disorders, 4th Edition (DSM-IV-TR) provides the following criteria for diagnosing ADHD[80]:

I. Some symptoms that cause impairment were present before age 7 years

II. Some impairment from the symptoms is present in 2 or more settings (eg, at school/work and at home)

III. There must be clear evidence of significant impairment in social, school, or work functioning

IV. Symptoms do not happen only during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder, and the symptoms are not better accounted for by another mental disorder (eg, mood disorder, anxiety disorder, dissociative disorder, or a personality disorder)

Conditions for set A or set B below must also be met to justify the diagnosis of ADHD:

A. Six or more of the following symptoms of inattention have been present for at least 6 months to a point that is disruptive and inappropriate for developmental level:

1. Often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
2. Often has trouble keeping attention on tasks or play activities.
3. Often does not seem to listen when spoken to directly.
4. Often does not follow instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions).
5. Often has trouble organizing activities.

6. Often avoids, dislikes, or doesn't want to do things that take a lot of mental effort for a long period of time (such as schoolwork or homework).
7. Often loses things needed for tasks and activities (eg, toys, school assignments, pencils, books, or tools).
8. Is often easily distracted.
9. Is often forgetful in daily activities.

B. Six or more of the following symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for developmental level:

Hyperactivity

1. Often fidgets with hands or feet or squirms in seat.
2. Often gets up from seat when remaining in seat is expected.
3. Often runs about or climbs when and where it is not appropriate (adolescents or adults may feel very restless).
4. Often has trouble playing or enjoying leisure activities quietly.
5. Is often "on the go" or often acts as if "driven by a motor".
6. Often talks excessively.

Impulsivity

1. Often blurts out answers before questions have been finished.
2. Often has trouble waiting one's turn.
3. Often interrupts or intrudes on others (eg, butts into conversations or games).

Based on these criteria, 3 types of ADHD have been identified:

1. ADHD, Combined Type: if both criteria A and B are met for the past 6 months
2. ADHD, Predominantly Inattentive Type: if criterion A is met but criterion B is not met for the past 6 months
3. ADHD, Predominantly Hyperactive-Impulsive Type: if criterion B is met but criterion A is not met for the past 6 months

3.3 Concerns About Improper Diagnosis of ADHD

Continued questioning of the validity of a diagnosis of ADHD has created uncertainties about its management in the minds of many clinicians and the public.[81] Because there is no diagnostically definitive test for ADHD, assessments must be comprehensive and involve multiple domains, informants, methods, and settings to determine whether the subject has ADHD or another disorder.[82, 83] Therefore, close attention must be paid to any potential underlying or associated medical, processing, emotional, and psychosocial problems.[84]

In terms of the frequency of ADHD diagnosis, one study reported that there is little evidence of widespread over-diagnosis or misdiagnosis of ADHD or of widespread over-prescription of methylphenidate by physicians.[8] However, despite the specific diagnostic criteria and the availability of effective pharmacologic treatments for children diagnosed with ADHD, a review of US prescription practices indicates that as few as 25% to 50% of these patients receive even minimal medical treatment for this condition.[85]

The prevalence of ADHD in African Americans is most likely similar to that found in the general population, whereas for Hispanics the prevalence is lower. Many African Americans and Hispanics are untreated and undiagnosed.[86]

The Council of Scientific Affairs of the American Medical Association had previously concluded that there was little evidence of widespread misdiagnosis of ADHD.[87] The probability of misdiagnosis increases with the fact that many children diagnosed with ADHD may also have bipolar disorder.[88] Though the population of pediatric bipolar illness may be small, research points to early misdiagnosis of ADHD, which may in fact be a presentation of mania.[89]

3.4 National Trends in the Diagnosis and Treatment of ADHD

Several studies have measured the trends in the diagnosis and treatment of ADHD. A 2003 study based on the National Medical Expenditure Survey and the National Medical Expenditure Panel Survey showed a significant increase in the overall rate of outpatient treatment of childhood ADHD between 1987 and 1997.[90] The rate of outpatient treatment increased from 0.9 per 100 children in 1987 to 3.4 per 100 children in 1997. Although the rate of treatment increased across all socio-demographic groups, there appears to have been a significant improvement in access to care for children from lower-income families.

The authors have hypothesized that several factors have contributed to the increasing diagnosis of ADHD, including a growing public awareness of ADHD; advocacy by national organizations composed of patients, families, and teachers; as well as efforts by the federal government and professional organizations. In 1991, the US Department of Education specifically recognized that students with ADHD could be considered disabled and eligible for special education services, which may have helped to increase the recognition of ADHD within the school setting.

4 METHYLPHENIDATE IS AN EFFECTIVE OPTION FOR TREATING ADHD

In children with ADHD, methylphenidate is effective in improving the symptoms of the disorder, with reduced off-task behavior and gross motor hyperactivity, improved compliance with supervising adults, and reduced aggressiveness as shown in multiple controlled studies.[91-95]

Positive outcomes in social behavior, academic performance, and cognitive functioning also have been demonstrated.[65, 96-98] Response rates in children with ADHD ranged from 69% to 77% for methylphenidate treatment, with placebo response rates of 2% to 24%;[91] the response rates also vary depending upon the outcome measures used.

4.1 Side Effects of Stimulants Used for Treatment of ADHD in Children

A systematic analysis of the ADHD literature revealed that many of the side effects associated with stimulant use may be relatively mild and of short duration, and will respond to dosing or timing adjustments.[99] The most commonly reported adverse events from the use of methylphenidate are insomnia, loss of appetite[28, 92] and headache.[100] Attempts to use other stimulants to treat ADHD, for example, theophylline,[101] selegiline,[100] and modafinil,[102] have resulted in similar side effects.

4.2 Side Effects of Non-Stimulants Used for Treatment of ADHD in Children

Several non-stimulant drugs have been used for the treatment of ADHD in clinical trial settings. Tricyclic antidepressants (TCAs) have been associated with anticholinergic and antihistamine effects,[28] whereas a comparison between atomoxetine and methylphenidate revealed that atomoxetine caused more vomiting, somnolence, and weight loss than methylphenidate.[103] The use of bupropion caused headache, gastrointestinal problems, and

insomnia, but these were statistically insignificant over placebo.[104] Although clonidine has been used in conjunction with stimulant treatments of ADHD to counteract the onset of insomnia, the primary side effect of clonidine is sedation[105]; also, several reports of cardiovascular-related adverse events have been documented with the use of clonidine.[106]

4.3 Findings of the Multimodal Treatment Study of Children With ADHD (MTA Study)

The National Institute of Mental Health and Department of Education-sponsored MTA Study confirmed the utility of careful medication management.[107] Children with combined-type ADHD were randomized to 1 of 4 treatment regimens: medication regimen (which consisted of intensively titrated, double-blind methylphenidate treatment); intensive behavioral treatment regimen with parent; school and child components; combined treatment regimen; and standard community treatment regimen (which could include pharmacotherapy). While all treatment groups experienced symptomatic improvement over the course of the study,[108] children on the medication regimen and the combined regimen experienced significantly more improvement in ADHD symptoms than those receiving intensive behavioral treatment or standard community treatment, even though 66% of the children in the community treatment arm received pharmacotherapy. A recently published 24-month follow-up of the MTA Study showed persistent superiority of the intensive medical management regimen over the behavioral regimen.[109]

5 POTENTIAL RISKS WITH METHYLPHENIDATE TREATMENT

While recognizing the beneficial effects of stimulant products, at two recent Advisory Committee meetings the FDA highlighted its concerns regarding serious cardiovascular and psychiatric adverse events reported with stimulant treatment.

5.1 Cardiovascular Risks

In CONCERTA controlled clinical trials, no deaths, including sudden deaths, myocardial infarctions or strokes were reported. At the recent Drug Safety and Risk Management Committee in February 2006, the postmarketing cardiovascular events reviewed for amphetamines and for methylphenidate included death and sudden death, and non-fatal, serious cardiovascular and cerebrovascular events.

The data presented by the FDA at the February 2006 meeting were based on the AERS database and are presented below in Table 5.1.[110] In order to calculate reporting rates for these events and to compare them to the general population rates, we converted the number of methylphenidate prescriptions (44,692,761) to 3,724,396 patient-years of exposure assuming a prescription is for a one-month supply of medication.

The voluntary nature of the FDA AERS reporting system has significant limitations, therefore, reporting rates may underestimate the true incidence rate by a factor of 10 or more.

Table 5-1. Postmarketing Pediatric Reports and Reporting Rates for Non-Excluded Deaths, Sudden Deaths and Serious, Non-Fatal Cardiovascular Adverse Events Reported With Methylphenidate Treatment (1999 Through 2003)

Report type	Number of reports	Reports per million prescriptions	Calculated rate per 100,000 P-Y [a]
Non-excluded death	10	0.22	0.27
Sudden death	7	0.16	0.19
Serious, non-fatal CV events	8	0.18	0.22

Abbreviations: CV, cardiovascular; P-Y, patient-years.
a: Reports per million prescriptions was calculated assuming one prescription represents a one-month supply for a patient.

For reference, the background rate of sudden death in the United States is estimated to be 1.3 to 8.5 per 100,000 patient-years in the pediatric and young adult population (less than 21 years of age).[111] If a correction is made for initially capturing only 10% of true events, the corrected reporting rate of sudden deaths of 1.9 per 100,000 patient-years is within the range of the background rate.

Mild increases in blood pressure and heart rate have been observed in clinical trials in children and adolescents and are already identified in the label. The long-term consequences of these short-term observations are unknown.

5.2 Psychiatric Risks

At the June 2005 Pediatric Advisory Committee meeting, FDA presented the 20 most frequently reported pediatric adverse events in the FDA AERS database for CONCERTA from launch (August, 2000) through 2003. These included the following psychiatric events: aggression, abnormal behavior, agitation, hallucination, anxiety, depression and suicidal ideation.[112] Some of these adverse events, for example suicidal ideation, reported with stimulant treatment in patients with ADHD are confounded because of the high frequency of

comorbid conditions and the prevalence of suicidal behaviors in the general adolescent population.

The estimated reporting rate for suicidal ideation from launch through 2004 with CONCERTA was calculated to be 0.65 per 100,000 patient-years. In 2004, the FDA reported 10 instances of suicidal ideation. Assuming that during that year only 10% of the 200,000 prescriptions per month represent high school aged adolescents, the estimated prevalence of suicidal ideation is 0.05%. If a correction is made for initially capturing only 10% of all events, the corrected prevalence of suicidal ideation is 0.5% in the CONCERTA-treated patients, compared to a prevalence rate of 16.5% in all US high school aged children.

While suicide was not part of the 20 most frequently reported adverse events, suicide has the most serious consequence. Although a modest association of ADHD and suicide has been reported (a relative risk of 2.91),[113] the presence of additional well-documented risk factors (comorbidities) such as depressive disorders, antisocial behaviors (conduct disorder) anxiety disorders and substance use disorder substantially confounds the interpretation of reports of suicidality, suicide attempts and completions.

Although there are fewer than 10 reported suicides with CONCERTA in our postmarketing database, in controlled trials, there are no reported completed suicides with CONCERTA. There is some evidence that long-term treatment with methylphenidate, particularly at higher doses, is associated with fewer suicide attempts and a reduced rate of substance use disorder, a major risk factor for suicide.[114, 115] This evidence may explain why, the reported rates of suicidality, suicide attempts, and completed suicides with stimulant treatment are substantially lower than those rates in the general population.

5.2.1 Prevalence and Incidence of Suicidal Behavior

An analysis of the National Comorbidity Survey and the National Comorbidity Survey Replication found that, despite significant increases in treatment, the 12-month prevalence rates of suicidal ideation, suicide plans, suicide gestures, and suicide attempts in adults in the United States has not significantly changed in the last decade. Overall, suicidal ideation occurs most frequently, with a 12-month prevalence rate of 3.3%.[116] The most recent data from the Youth Risk Behavior Surveillance System found the 12-month prevalence rate for suicide attempts in adolescents in high school in the United States to be 8.5%. The 12-month prevalence rate for suicidal ideation was 16.5%.[117] The actual suicide rate in children 10 to 19 years of age, reported by the Centers for Disease Control and Prevention, has decreased from 6.2 per 100,000 in 1992 to 4.6 per 100,000 in 2001.[118]

DSM-IV psychiatric disorders are risk factors for suicidal behavior, particularly any anxiety disorder (12-month prevalence of suicidal ideation of 60.6%) and major depressive disorder (12-month prevalence of suicidal ideation of 38.9%). The diagnosis of attention-deficit/ hyperactivity disorder, conduct disorder, or oppositional defiance disorder are associated with 12-month prevalence rates of suicidal ideation of 14.4%, 3.0%, or 9.4%, respectively.[116]

The incidence of adults who admit to suicidal ideation in the United States is estimated to be 3000 per 100,000, the estimated incidence of suicide attempts is 500 per 100,000; the suicide rate is 14 per 100,000.[116] Suicidal behavior is underreported, and the actual rate of these events is likely to be higher. Although less information is available regarding suicidal behavior rates in children and adolescents, it is known that the rates of suicidal behavior is 2 to 3 times higher in adolescents than in adults.[14] There is a marked

difference in suicide rates by age groups in the pediatric population; in 1994, the suicide rates for ages 5 to 14 and 15 to 24 were 0.9 and 13.8 per 100,000, respectively.[119]

5.3 Risk Communication in Product Labeling

The following contraindications and warnings related to cardiovascular and psychiatric adverse events that are included in the labeling of CONCERTA (methylphenidate HCl) extended-release tablets; the entire label is provided in Attachment 1:

CONTRAINDICATIONS:

CONCERTA is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

CONCERTA is contraindicated in patients with motor tics or a family history of Tourette's syndrome.

WARNINGS:

Depression

CONCERTA should not be used to treat severe depression.

Psychosis

Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

Sudden Death and Pre-existing Structural Cardiac Abnormalities

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children with structural cardiac abnormalities. Although some structural cardiac abnormalities alone may carry an increased risk of sudden death, stimulant products generally should not be used in children, adolescents, or adults with known structural cardiac abnormalities.

Hypertension and other Cardiovascular Conditions

Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, eg, those with preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism. Blood pressure

should be monitored at appropriate intervals in patients taking CONCERTA®, especially patients with hypertension.

In the laboratory classroom clinical trials in children (Studies 1 and 2), both CONCERTA® qd and methylphenidate tid increased resting pulse by an average of 2-6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1-4 mm Hg during the day, relative to placebo.

In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with CONCERTA® and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for CONCERTA® and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively.

6 SUMMARY OF BENEFITS AND RISKS

At the recent Drug Safety and Risk Management Committee in February 2006, the postmarketing cardiovascular events reviewed for amphetamines and for methylphenidate included death and sudden death, and non-fatal, serious cardiovascular and cerebrovascular events. An analysis of the serious adverse events showed reporting rates that are less than one event per million methylphenidate prescriptions. Even with a many-fold correction for under-reporting in the passive surveillance system, the observed rate of sudden deaths is consistent with the background rate.

Mild increases in blood pressure and heart rate have been observed in clinical trials in children and adolescents and are already identified in the labeling. The long-term consequences of these short-term observations are unknown.

Suicidal ideation was reported as one type of the top 20 reported events in the FDA's June 2005 CONCERTA postmarketing safety review; suicide was not. Psychiatric adverse events reported with stimulant treatment in patients with ADHD may be confounded because of the high frequency of comorbid conditions in patients with ADHD. Although there have

been fewer than 10 reported suicides in our postmarketing database, in controlled clinical trials, there were no reported suicides with CONCERTA. There is some evidence that long-term treatment with methylphenidate, particularly at higher doses, is associated with fewer suicide attempts and a reduced rate of substance use disorder, a major risk factor for suicide. This evidence may explain why the reported rates of suicidality, suicide attempts, and completed suicides with stimulant treatment are substantially lower than those rates in the general population.

It is customary to balance the therapeutic benefits and potential risks a patient is exposed to during treatment. Untreated ADHD is associated with severe consequences. Clinical trials have shown that methylphenidate is effective in improving the symptoms of the disorder in children, adolescents, and adults. Benefits to patients are numerous and have a significant positive impact on the patient's quality of life (QOL). As no pharmacologic treatment is without risk, patients who are receiving methylphenidate may be exposed to some increased risk of adverse events. Although cognizant of the beneficial effects of methylphenidate, the FDA has recently highlighted concerns regarding serious cardiovascular and psychiatric adverse events reported with ADHD medications. In January 2006, FDA requested that all stimulant products include an additional warning regarding the possibility of sudden death in patients with structural cardiac abnormalities.

The current labeling for CONCERTA contains clear contraindications and warnings related to cardiovascular and psychiatric adverse events reported with the use of methylphenidate.

While much of the literature intended to discredit ADHD and its treatment is polemical and alarmist in nature, genuine attempts to untangle the controversies surrounding this disorder have been and continue to be made.

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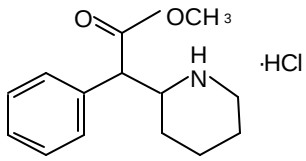
ATTACHMENT 1

CONCERTA® (methylphenidate HCl)
Extended-release Tablets CII

DESCRIPTION

CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. Chemically, methylphenidate HCl is d,l (racemic) methyl a-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is $C_{14}H_{19}NO_2 \bullet HCl$. Its structural formula is:



Methylphenidate HCl USP is a white, odorless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

CONCERTA® also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin.

System Components and Performance

CONCERTA® uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within one hour, providing an initial dose of methylphenidate. Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The membrane controls the rate at which

water enters the tablet core, which in turn controls drug delivery. Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug concentration gradient incorporated into the two drug layers of CONCERTA®. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell along with insoluble core components. It is possible that CONCERTA® extended-release tablets may be visible on abdominal x-rays under certain circumstances, especially when digital enhancing techniques are utilized.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Methylphenidate HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

Pharmacokinetics

Absorption

Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins. Mean times to reach peak plasma concentrations across all doses of CONCERTA® occurred between 6 to 10 hours.

CONCERTA® qd minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate tid (see Figure 1). The relative bioavailability of CONCERTA® qd and methylphenidate tid in adults is comparable.

FIGURE 1

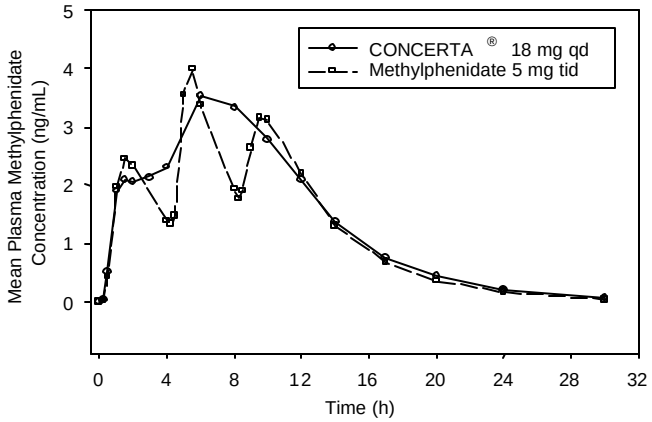


Figure 1. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of CONCERTA® 18 mg qd and immediate-release methylphenidate 5 mg tid administered every 4 hours.

The mean pharmacokinetic parameters in 36 adults following the administration of CONCERTA® 18 mg qd and methylphenidate 5 mg tid are summarized in Table 1.

TABLE 1
Mean ± SD Pharmacokinetic Parameters

Parameters	CONCERTA® (18 mg qd) (n=36)	Methylphenidate (5 mg tid) (n=35)
C_{max} (ng/mL)	3.7 ± 1.0	4.2 ± 1.0
T_{max} (h)	6.8 ± 1.8	6.5 ± 1.8
AUC_{inf} (ng•h/mL)	41.8 ± 13.9	38.0 ± 11.0
$t_{½}$ (h)	3.5 ± 0.4	3.0 ± 0.5

No differences in the pharmacokinetics of CONCERTA® were noted following single and repeated once-daily dosing indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated once-daily dosing are similar to those following the first dose of CONCERTA® 18 mg.

Dose Proportionality

Following administration of CONCERTA® in single doses of 18, 36, and 54 mg/day to adults, C_{max} and $AUC_{(0\text{-}inf)}$ of d-methylphenidate were proportional to dose, whereas l-methylphenidate C_{max} and $AUC_{(0\text{-}inf)}$ increased disproportionately with respect to dose.

Following administration of CONCERTA®, plasma concentrations of the l-isomer were approximately 1/40th the plasma concentrations of the d-isomer.

In a multiple-dose study in adolescent ADHD patients aged 13 to 16 administered their prescribed dose (18 to 72 mg/day) of CONCERTA®, mean C_{max} and AUC_{TAU} of d- and total methylphenidate increased proportionally with respect to dose.

Distribution

Plasma methylphenidate concentrations in adults and adolescents decline biexponentially following oral administration. The half-life of methylphenidate in adults and adolescents following oral administration of CONCERTA® was approximately 3.5 h.

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily by de-esterification to a-phenyl-piperidine acetic acid (PPA), which has little or no pharmacologic activity. In adults the metabolism of CONCERTA® qd as evaluated by metabolism to PPA is similar to that of methylphenidate tid. The metabolism of single and repeated once-daily doses of CONCERTA® is similar.

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

Food Effects

In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of CONCERTA® when administered after a high fat breakfast. There is no evidence of dose dumping in the presence or absence of food.

Special Populations

Gender

In healthy adults, the mean dose-adjusted $AUC_{(0\text{-}inf)}$ values for CONCERTA® were 36.7 ng•h/mL in men and 37.1 ng•h/mL in women, with no differences noted between the two groups.

Race

In adults receiving CONCERTA®, dose-adjusted $AUC_{(0\text{-}inf)}$ was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age

Increase in age resulted in increased apparent oral clearance (CL/F) (58% increase in adolescents compared to children). Some of these differences could be explained by body weight differences among these populations. This suggests that subjects with higher body weight may have lower exposures of total methylphenidate at similar doses.

The pharmacokinetics of CONCERTA® has not been studied in children less than 6 years of age.

Renal Insufficiency

There is no experience with the use of CONCERTA® in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of CONCERTA®.

Hepatic Insufficiency

There is no experience with the use of CONCERTA® in patients with hepatic insufficiency.

Clinical Studies

CONCERTA was demonstrated to be effective in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in 4 randomized, double-blind, placebo-controlled studies in children and adolescents who met the Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD.

Children

Three double blind, active- and placebo-controlled studies were conducted in 416 children aged 6 to 12. The controlled studies compared CONCERTA® given qd (18, 36, or 54 mg), methylphenidate given tid over 12 hours (15, 30, or 45 mg total daily dose), and placebo in two single-center, 3-week crossover studies (Studies 1 and 2) and in a multicenter, 4-week, parallel-group comparison (Study 3). The primary comparison of interest in all three trials was CONCERTA® versus placebo.

Symptoms of ADHD were evaluated by community schoolteachers using the Inattention / Overactivity with Aggression (IOWA) Conners scale. Statistically significant reduction in the Inattention / Overactivity subscale versus placebo was shown consistently across all three controlled studies for CONCERTA®. The scores for CONCERTA® and placebo for the three studies are presented in Figure 2.

FIGURE 2
Mean (SEM) Community School Teacher IOWA Conners
Inattention/Overactivity Scores

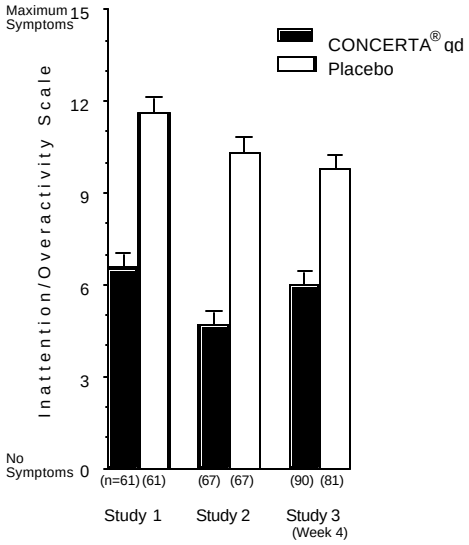
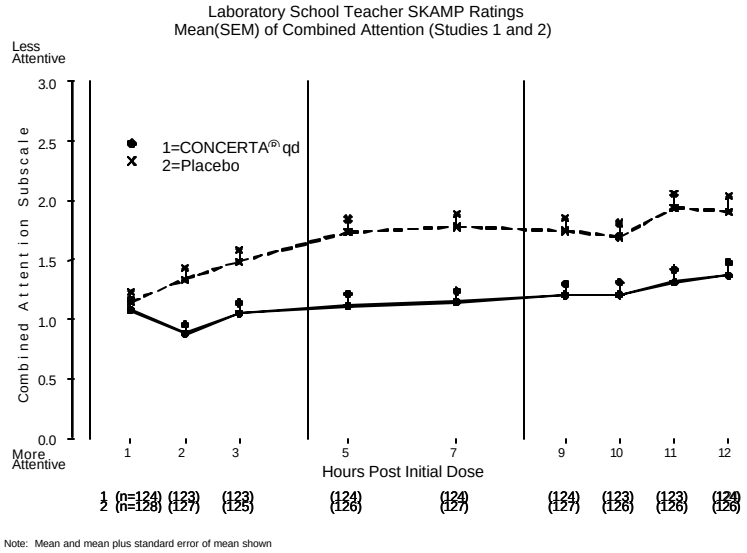


Figure 2: Mean Community School Teacher IOWA Conners Inattention/Overactivity Scores with CONCERTA® once-daily (18, 36, or 54 mg) and placebo. Studies 1 and 2 involved a 3-way crossover of 1 week per treatment arm. Study 3 involved 4 weeks of parallel group treatments with a Last Observation Carried Forward analysis at week 4. Error bars represent the mean plus standard error of the mean.

In Studies 1 and 2, symptoms of ADHD were evaluated by laboratory schoolteachers using the SKAMP* laboratory school rating scale. The combined results from these two studies demonstrated significant improvements in attention and behavior in patients treated with CONCERTA® versus placebo that were maintained through 12 hours after dosing. Figure 3 presents the laboratory schoolteacher SKAMP ratings for CONCERTA® and placebo.
*Swanson, Kotkin, Agler, M-Fynn and Pelham

FIGURE 3



Note: Mean and mean plus standard error of mean shown

Adolescents

In a randomized, double blind, multi-center, placebo-controlled trial (Study 4) involving 177 patients, CONCERTA® was demonstrated to be effective in the treatment of ADHD in adolescents aged 13 to 18 at doses up to 72 mg/day (1.4 mg/kg/day). Of 220 patients who entered an open 4-week titration phase, 177 were titrated to an individualized dose (maximum of 72 mg/day) based on meeting specific improvement criteria on the ADHD Rating Scale and the Global Assessment of Effectiveness with acceptable tolerability. Patients who met these criteria were then randomized to receive either their individualized dose of CONCERTA® (18 – 72 mg/day, n=87) or placebo (n=90) during a two-week double-blind phase. At the end of this phase, mean scores for the investigator rating on the ADHD Rating Scale demonstrated that CONCERTA® was significantly superior to placebo

INDICATION AND USAGE

Attention Deficit Hyperactivity Disorder (ADHD)

CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of CONCERTA® in the treatment of ADHD was established in three controlled trials of children aged 6-12 and in one controlled trial in adolescents aged 13-17. All patients met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY).

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, eg, in social, academic, or occupational functioning, and be present in two or more settings, eg, school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

CONCERTA® is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Stimulants are not intended for use in patients who exhibit symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Long-Term Use

The effectiveness of CONCERTA® for long-term use, ie, for more than 4 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use CONCERTA® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Agitation

CONCERTA® is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate

CONCERTA® is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma

CONCERTA® is contraindicated in patients with glaucoma.

Tics

CONCERTA® is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see ADVERSE REACTIONS).

Monoamine Oxidase Inhibitors

CONCERTA® is contraindicated during treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a MAO-inhibitor (hypertensive crises may result) (see PRECAUTIONS, Drug Interactions).

WARNINGS

Depression

CONCERTA® should not be used to treat severe depression.

Fatigue

CONCERTA® should not be used for the prevention or treatment of normal fatigue states.

Long-Term Suppression of Growth

Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may cause suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

Psychosis

Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

Seizures

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Potential for Gastrointestinal Obstruction

Because the CONCERTA® tablet is nondeformable and does not appreciably change in shape in the GI tract, CONCERTA® should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA® should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients).

Sudden Death and Pre-existing Structural Cardiac Abnormalities

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children with structural cardiac abnormalities. Although some structural cardiac abnormalities alone may carry an increased risk of sudden death, stimulant products generally should not be used in children, adolescents, or adults with known structural cardiac abnormalities.

Hypertension and other Cardiovascular Conditions

Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, eg, those with preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism. Blood pressure should be monitored at appropriate intervals in patients taking CONCERTA®, especially patients with hypertension.

In the laboratory classroom clinical trials in children (Studies 1 and 2), both CONCERTA® qd and methylphenidate tid increased resting pulse by an average of 2-6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1-4 mm Hg during the day, relative to placebo.

In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with CONCERTA® and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for CONCERTA® and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively.

Visual Disturbance

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Use in Children Under Six Years of Age

CONCERTA® should not be used in children under six years, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE

CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

Hematologic Monitoring

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

Information for Patients

Patients should be informed that CONCERTA® should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Patient information is printed at the end of this insert. To assure safe and effective use of CONCERTA®, the information and instructions provided in the patient information section should be discussed with patients.

Drug Interactions

CONCERTA® should not be used in patients being treated (currently or within the proceeding 2 weeks) with MAO inhibitors (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors).
Because of possible increases in blood pressure, CONCERTA® should be used cautiously with vasopressor agents.

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

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

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

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

carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the in vitro Ames reverse mutation assay or the in vitro mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an in vitro assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative in vivo in males and females in the mouse bone marrow micronucleus assay.

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively.

Pregnancy: Teratogenic Effects

Pregnancy Category C: Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPA in pregnant rats was 2 times that seen in trials in volunteers and patients with the maximum recommended dose of CONCERTA® based on the AUC.

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

Nursing Mothers

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

Pediatric Use

The safety and efficacy of CONCERTA® in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (see WARNINGS).

ADVERSE REACTIONS

The development program for CONCERTA® included exposures in a total of 2121 participants in clinical trials (1797 patients, 324 healthy adult subjects). These participants received CONCERTA® 18, 36, 54 and/or 72 mg/day. Children, adolescents, and adults with ADHD were evaluated in four controlled clinical studies, three open-label clinical studies and two clinical pharmacology studies. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events.

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

Adverse Findings in Clinical Trials with CONCERTA®

Adverse Events Associated with Discontinuation of Treatment

In the 4-week placebo-controlled, parallel-group trial in children (Study 3) one CONCERTA®-treated patient (0.9%; 1/106) and one placebo-treated patient (1.0%; 1/99) discontinued due to an adverse event (sadness and increase in tics, respectively).

In the 2-week placebo-controlled phase of a trial in adolescents (Study 4), no CONCERTA®-treated patients (0%; 0/87) and 1 placebo-treated patient (1.1%; 1/90) discontinued due to an adverse event (increased mood irritability).

In the two open-label, long-term safety trials (Studies 5 and 6: one 24-month study in children aged 6 to 13 and one 9-month study in child, adolescent and adult patients treated with CONCERTA®) 6.7% (101/1514) of patients discontinued due to adverse events.

These events with an incidence of >0.5% included: insomnia (1.5%), twitching (1.0%), nervousness (0.7%), emotional lability (0.7%), abdominal pain (0.7%), and anorexia (0.7%).

Treatment-Emergent Adverse Events Among CONCERTA®-Treated Patients

Table 2 enumerates, for a 4-week placebo-controlled, parallel-group trial (Study 3) in children with ADHD at CONCERTA® doses of 18, 36, or 54 mg/day, the incidence of treatment-emergent adverse events. The table includes only those events that occurred in 1% or more of patients treated with CONCERTA® where the incidence in patients treated with CONCERTA® was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 2
Incidence of Treatment-Emergent Events[1] in a 4-Week Placebo-Controlled Clinical Trial of CONCERTA® In Children

Body System	Preferred Term	CONCERTA® (n=106)	Placebo (n= 99)
General	Headache	14 %	10 %
	Abdominal pain (stomachache)	7 %	1 %
Digestive	Vomiting	4 %	3 %
	Anorexia (loss of appetite)	4 %	0 %
Nervous	Dizziness	2 %	0 %
	Insomnia	4 %	1 %
Respiratory	Upper Respiratory Tract Infection	8 %	5 %
	Cough Increased	4 %	2 %
	Pharyngitis	4 %	3 %
	Sinusitis	3 %	0 %

1. Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 1% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Table 3 lists the incidence of treatment-emergent adverse events for a 2-week placebo-controlled trial (Study 4) in adolescents with ADHD at CONCERTA® doses of 18, 36, 54 or 72 mg/day.

TABLE 3
Incidence of Treatment-Emergent Events[1] in a 2-Week Placebo-Controlled Clinical Trial of CONCERTA® in Adolescents

Body System	Preferred Term	CONCERTA (n=87)	Placebo (n=90)
General	Accidental injury	6 %	3 %
	Fever	3 %	0 %
	Headache	9 %	8 %
Digestive	Anorexia	2 %	0 %
	Diarrhea	2 %	0 %
	Vomiting	3 %	0 %
Nervous	Insomnia	5 %	0 %
Respiratory	Pharyngitis	2 %	1 %
	Rhinitis	3 %	2 %
Urogenital	Dysmenorrhea	2 %	0 %

1. Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 2% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Tics

In a long-term uncontrolled study (n=432 children), the cumulative incidence of new onset of tics was 9% after 27 months of treatment with CONCERTA®.

In a second uncontrolled study (n=682 children) the cumulative incidence of new onset tics was 1% (9/682 children). The treatment period was up to 9 months with mean treatment duration of 7.2 months.

Post-Marketing Experience with CONCERTA®:

Additional very rare undesirable effects were reported during the marketing experience: difficulties in visual accommodation, blurred vision, abnormal liver function test (e.g., transaminase elevation), palpitations, arrhythmia, leucopenia, and thrombocytopenia.

Adverse Events with Other Methylphenidate HCl Products

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up

and down; tachycardia; angina; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: hepatic coma; isolated cases of cerebral arteritis and/or occlusion; anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

CONCERTA®, like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

Abuse, Dependence, and Tolerance

See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE

Signs and Symptoms

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

Recommended Treatment

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a

cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for CONCERTA® overdosage has not been established.

The prolonged release of methylphenidate from CONCERTA® should be considered when treating patients with overdose.

Poison Control Center

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

DOSAGE AND ADMINISTRATION

CONCERTA® should be administered orally once daily in the morning with or without food as it has been shown to improve attention and behavior through 12 hours after dosing.

CONCERTA® must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed (see PRECAUTIONS: Information for Patients).

Based on an assessment of clinical benefit and tolerability, doses may be increased at weekly intervals for patients who have not achieved an optimal response at a lower dose.

Patients New to Methylphenidate

The recommended starting dose of CONCERTA® for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily.

Patient Age	Recommended Starting Dose	Maximum Dosage
Children 6-12 years of age	18 mg/day	54 mg/day
Adolescents 13-17 years of age	18 mg/day	72 mg/day not to exceed 2 mg/kg/day

Patients Currently Using Methylphenidate

The recommended dose of CONCERTA® for patients who are currently taking methylphenidate bid or tid, at doses of 10 to 45 mg/day is provided in Table 4. Dosing recommendations are based on current dose regimen and clinical judgment. Initial conversion dosage should not exceed 54 mg daily. After conversion, dosages may be

adjusted to a maximum of 72 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

TABLE 4
Recommended Dose Conversion from
Methylphenidate Regimens to CONCERTA®

Previous Methylphenidate Daily Dose	Recommended CONCERTA® Starting Dose
5 mg Methylphenidate bid or tid	18 mg q am
10 mg Methylphenidate bid or tid	36 mg q am
15 mg Methylphenidate bid or tid	54 mg q am

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

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

Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with CONCERTA®. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods.

Nevertheless, the physician who elects to use CONCERTA® for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

HOW SUPPLIED

CONCERTA® (methylphenidate HCl) Extended-release Tablets are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow and imprinted with "alza 18". The 27 mg tablets are gray and imprinted with "alza 27". The 36 mg tablets are white and imprinted with "alza 36". The 54 mg tablets are brownish-red and imprinted with "alza 54". All four dosage strengths are supplied in bottles containing 100 tablets.

18 mg 100 count bottle	NDC 17314-5850-2
27 mg 100 count bottle	NDC 17314-5853-2
36 mg 100 count bottle	NDC 17314-5851-2
54 mg 100 count bottle	NDC 17314-5852-2

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from humidity.

REFERENCE

American Psychiatric Association. Diagnosis and Statistical Manual of Mental Disorders. 4th ed. Washington DC: American Psychiatric Association 1994.

Rx Only.

For more information call 1-888-440-7903 or visit www.concerta.net

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INFORMATION FOR PATIENTS TAKING CONCERTA® OR THEIR PARENTS OR CAREGIVERS

CONCERTA® (methylphenidate HCl) Extended-release Tablets CII

This information is for patients taking CONCERTA® Extended-release Tablets CII for the treatment of Attention Deficit Hyperactivity Disorder, or their parents or caregivers.

Please read this before you start taking CONCERTA®. Remember, this information does not take the place of your doctor's instructions. If you have any questions about this information or about CONCERTA®, talk to your doctor or pharmacist.

What is CONCERTA®?

CONCERTA® is a once-a-day treatment for Attention Deficit Hyperactivity Disorder, or ADHD. CONCERTA® contains the drug methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 30 years. CONCERTA® is taken by mouth, once each day in the morning.

What is Attention Deficit Hyperactivity Disorder?

ADHD has three main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all three types of symptoms.

Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis.

How does CONCERTA® work?

Part of the CONCERTA® tablet dissolves right after you swallow it in the morning, giving you an initial dose of methylphenidate. The remaining drug is slowly released with an increasing rate during the day to continue to help lessen the symptoms of ADHD. Methylphenidate, the active ingredient in CONCERTA®, helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Who should NOT take CONCERTA®?

You should NOT take CONCERTA® if:

- You have significant anxiety, tension, or agitation since CONCERTA® may make these conditions worse.
- You are allergic to methylphenidate or any of the other ingredients in CONCERTA®.
- You have glaucoma, an eye disease.
- You have tics or Tourette's syndrome, or a family history of Tourette's syndrome.

Talk to your doctor if you believe any of these conditions apply to you.

How should I take CONCERTA®?

Do not chew, crush, or divide the tablets. Swallow CONCERTA® tablets whole with the help of water or other liquids, such as milk or juice.

Take CONCERTA® once each day in the morning.

You may take CONCERTA® before or after you eat.

Take the dose prescribed by your doctor. Your doctor may adjust the amount of drug you take until it is right for you. From time to time, your doctor may interrupt your treatment to check your symptoms while you are not taking the drug.

What are the possible side effects of CONCERTA®?

In the clinical studies with patients using CONCERTA®, the most common side effects were headache, stomach pain, sleeplessness, and decreased appetite. Other side effects seen with methylphenidate, the active ingredient in CONCERTA®, include nausea, vomiting, dizziness, nervousness, tics, allergic reactions, increased blood pressure and psychosis (abnormal thinking or hallucinations).

This is not a complete list of possible side effects. Ask your doctor about other side effects. If you develop any side effect, talk to your doctor.

What must I discuss with my doctor before taking CONCERTA®?

Talk to your doctor ***before*** taking CONCERTA® if you:

- Are being treated for depression or have symptoms of depression such as feelings of sadness, worthlessness, and hopelessness.
- Have motion tics (hard-to-control, repeated twitching of any parts of your body) or verbal tics (hard-to-control repeating of sounds or words).
- Have someone in your family with motion tics, verbal tics, or Tourette's syndrome.
- Have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis.

- Have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms).
- Have high blood pressure.
- Have a narrowing or blockage of your gastrointestinal tract (your esophagus, stomach, or small or large intestine).

Tell your doctor immediately if you develop any of the above conditions or symptoms while taking CONCERTA®.

Can I take CONCERTA® with other medicines?

Tell your doctor about ***all*** medicines that you are taking. Your doctor should decide whether you can take CONCERTA® with other medicines. These include:

Other medicines that a doctor has prescribed.

Medicines that you buy yourself without a prescription.

Any herbal remedies that you may be taking.

You should not take CONCERTA® with monoamine oxidase (MAO) inhibitors.

While on CONCERTA®, do not start taking a new medicine or herbal remedy before checking with your doctor.

CONCERTA® may change the way your body reacts to certain medicines. These include medicines used to treat depression, prevent seizures, or prevent blood clots (commonly called "blood thinners"). Your doctor may need to change your dose of these medicines if you are taking them with CONCERTA®.

Other Important Safety Information

Abuse of methylphenidate can lead to dependence.

Tell your doctor if you have ever abused or been dependent on alcohol or drugs, or if you are now abusing or dependent on alcohol or drugs.

Before taking CONCERTA®, tell your doctor if you are pregnant or plan on becoming pregnant. If you take methylphenidate, it may be in your breast milk. Tell your doctor if you are nursing a baby.

Tell your doctor if you have blurred vision when taking CONCERTA®.

Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate in children. Your doctor will be carefully watching your height and weight. If you are not growing or gaining weight as your doctor expects, your doctor may stop your CONCERTA® treatment.

Call your doctor ***immediately*** if you take more than the amount of CONCERTA® prescribed by your doctor.

What else should I know about CONCERTA®?
CONCERTA® has not been studied in children under 6 years of age.

The CONCERTA® tablet does not dissolve completely after all the drug has been released, and you may sometimes notice it in your stool. This is normal.

CONCERTA® may be a part of your overall treatment for ADHD. Your doctor may also recommend that you have counseling or other therapy.

As with all medicines, never share CONCERTA® with anyone else and take only the number of CONCERTA® tablets prescribed by your doctor.

CONCERTA® should be stored in a safe place at room temperature (between 59°-86° F). Do not store this medicine in hot, damp, or humid places.

Keep out of the reach of children.

For more information call 1-888-440-7903 or visit www.concerta.net

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