CONCERTA® 18mg
CONCERTA® 27mg
CONCERTA® 36mg
CONCERTA® 54mg
Methylphenidate HCl, Extended-Release Tablets

FULL PRESCRIBING INFORMATION

WARNING: ABUSE, MISUSE, AND ADDICTION

CONCERTA has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including CONCERTA, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing CONCERTA, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug. Throughout CONCERTA treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction *[see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.2)]*.

1 INDICATIONS AND USAGE

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

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, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., 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.

1.1 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.

1.2 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). Drug treatment may not be indicated for all patients with ADHD. 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.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

CONCERTA should be administered orally once daily in the morning with or without food.

CONCERTA must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed *[see Patient Counseling Information (17)]*.

2.2 Patients New to Methylphenidate

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

Table 1. CONCERTA Recommended Starting Doses and Dose Ranges

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

2.3 Patients Currently Using Methylphenidate

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

Table 2. Recommended Dose Conversion from Methylphenidate Regimens to CONCERTA

Previous Methylphenidate Daily Dose	Recommended CONCERTA® Starting Dose
5 mg Methylphenidate twice daily or three times daily	18 mg every morning
10 mg Methylphenidate twice daily or three times daily	36 mg every morning
15 mg Methylphenidate twice daily or three times daily	54 mg every morning
20 mg Methylphenidate twice daily or three times daily	72 mg every morning

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

2.4 Dose Titration

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

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

2.5 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.

The effectiveness of CONCERTA for long-term use, i.e., for more than 7 weeks, has not been systematically evaluated in controlled trials. 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.

2.6 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.

3 DOSAGE FORMS AND STRENGTHS

CONCERTA (methylphenidate HCl) Extended-Release Tablets are available in the following dosage strengths: 18 mg tablets are yellow and imprinted with "alza 18," 27 mg tablets are gray and

imprinted with “alza 27,” 36 mg tablets are white and imprinted with “alza 36,” and 54 mg tablets are brownish-red and imprinted with “alza 54.”

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Methylphenidate

Hypersensitivity reactions, such as angioedema and anaphylactic reactions, have been observed in patients treated with CONCERTA. Therefore, CONCERTA is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product *[see Adverse Reactions (6.6)]*.

4.2 Tics

CONCERTA is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome *[see Adverse Reactions (6.4)]*.

4.3 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 Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Abuse, Misuse, and Addiction

CONCERTA has a high potential for abuse and misuse. The use of CONCERTA exposes individuals to the risks of abuse and misuse, which can lead to the development of a substance use disorder, including addiction. CONCERTA can be diverted for non-medical use into illicit channels or distribution *[see Drug Abuse and Dependence (9.2)]*. Misuse and abuse of CNS stimulants, including CONCERTA, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing CONCERTA, assess each patient’s risk for abuse, misuse, and addiction. Educate patients and their families about these risks and proper disposal of any unused drug. Advise patients to store CONCERTA in a safe place, preferably locked, and instruct patients to not give CONCERTA to anyone else. Throughout CONCERTA treatment, reassess each patient’s risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

5.2 Serious Cardiovascular Events

Sudden Death and Preexisting Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults

Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and Other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2 to 4 mm Hg) and average heart rate (about 3 to 6 bpm) *[see Adverse Reactions (6.5)]*, and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with preexisting hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Assessing Cardiovascular Status in Patients Being Treated with Stimulant Medications

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

5.3 Increased Blood Pressure and Heart Rate

CNS stimulants may cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). Some patients may have larger increases.

Monitor all CONCERTA-treated patients for hypertension and tachycardia.

5.4 Psychiatric Adverse Reactions

Exacerbation of Pre-existing Psychosis

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a manic or mixed episode in patients. Prior to initiating CONCERTA treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms

CNS stimulants, at the recommended dosage, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared with 0% of placebo-treated patients. If such symptoms occur, consider discontinuing CONCERTA.

5.5 Seizures

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

5.6 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidateuse in both adult and pediatric male patients *[see Adverse Reactions (6.6)]*. Although priapism was not reported with methylphenidate initiation, it developed after some time on methylphenidate, often subsequent to an increase in dosage. Priapism also occurred during methylphenidate withdrawal (drug holidays or during discontinuation).

CONCERTA-treated patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

5.7 Peripheral Vasculopathy, including Raynaud's Phenomenon

CNS stimulants, including CONCERTA, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, sequelae have included digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports and at the therapeutic dosages of CNS stimulants in all age groups throughout the course of treatment. Signs and symptoms generally improved after dosage reduction or discontinuation of the CNS stimulant.

Careful observation for digital changes is necessary during CONCERTA treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for CONCERTA-treated patients who develop signs or symptoms of peripheral vasculopathy.

5.8 Long-Term Suppression of Growth in Pediatric Patients

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

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or nonmedication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and nonmedication-treated children over 36 months (to the ages of 10 to 13 years), suggests that pediatric patients who received methylphenidate for 7 days per week throughout the year had a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this development period. Closely monitor growth (weight and height) in CONCERTA-treated pediatric patients. Pediatric patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

5.9 Potential for Gastrointestinal Obstruction

Because the 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 pseudo-obstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA should be used only in patients who are able to swallow the tablet whole *[see Patient Counseling Information (17)]*.

5.10 Hematologic Monitoring

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

5.11 Acute Angle Closure Glaucoma

There have been rare reports of angle closure glaucoma associated with methylphenidate treatment.

Although the mechanism is not clear, CONCERTA-treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist.

5.12 Increased Intraocular Pressure and Glaucoma

There have been reports of an elevation of intraocular pressure (IOP) associated with methylphenidate treatment *[see Adverse Reactions (6.6)]*.

Prescribe CONCERTA to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Closely monitor CONCERTA-treated patients with a history of abnormally increased IOP or open angle glaucoma.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Abuse, Misuse, and Addiction *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Hypersensitivity to Methylphenidate *[see Contraindications (4.1)]*
- Tics *[see Contraindications (4.2)]*
- Monoamine Oxidase Inhibitors *[see Contraindications (4.3) and Drug Interactions (7.1)]*
- Serious Cardiovascular Events *[see Warnings and Precautions (5.2)]*
- Increased Blood Pressure and Heart Rate *[see Warnings and Precautions (5.3)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Seizures *[see Warnings and Precautions (5.5)]*
- Priapism *[see Warnings and Precautions (5.6)]*
- Peripheral Vasculopathy, including Raynaud's Phenomenon *[see Warnings and Precautions (5.7)]*
- Long-Term Suppression of Growth in Pediatric Patients *[see Warnings and Precautions (5.8)]*
- Potential for Gastrointestinal Obstruction *[see Warnings and Precautions (5.9)]*
- Hematologic Monitoring *[see Warnings and Precautions (5.10)]*

- Acute Angle Closure Glaucoma *[see Warnings and Precautions (5.11)]*
- Increased Intraocular Pressure and Glaucoma *[see Warnings and Precautions (5.12)]*

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

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

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

Table 3. CONCERTA Exposure in Double-Blind and Open-Label Clinical Studies

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

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

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

Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of CONCERTA based on the comprehensive assessment of the available adverse event information. A causal association for CONCERTA often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials

of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

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

6.1 Commonly Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials

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

Children and Adolescents

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

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

System/Organ Class Adverse Reaction	**CONCERTA (n=321) %**	**Placebo (n=318) %**
Gastrointestinal Disorders		
Abdominal pain upper	6.2	3.8
Vomiting	2.8	1.6
General Disorders and Administration Site Conditions		
Pyrexia	2.2	0.9
Infections and Infestations		
Nasopharyngitis	2.8	2.2
Nervous System Disorders		
Dizziness	1.9	0
Psychiatric Disorders		
Insomnia*	2.8	0.3
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1.9	0.9
Oropharyngeal pain	1.2	0.9

*Terms of Initial insomnia (CONCERTA=0.6%) and Insomnia (CONCERTA=2.2%) are combined into Insomnia.

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

Adults

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

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

System/Organ Class Adverse Reaction	**CONCERTA (n=415)** %	**Placebo (n=212)** %
Cardiac Disorders		

System/Organ Class Adverse Reaction	CONCERTA (n=415) %	Placebo (n=212) %
Tachycardia	4.8	0
Palpitations	3.1	0.9
Ear and Labyrinth Disorders		
Vertigo	1.7	0
Eye Disorders		
Vision blurred	1.7	0.5
Gastrointestinal Disorders		
Dry mouth	14.0	3.8
Nausea	12.8	3.3
Dyspepsia	2.2	0.9
Vomiting	1.7	0.5
Constipation	1.4	0.9
General Disorders and Administration Site Conditions		
Irritability	5.8	1.4
Infections and Infestations		
Upper respiratory tract infection	2.2	0.9
Investigations		
Weight decreased	6.5	3.3
Metabolism and Nutrition Disorders		
Decreased appetite	25.3	6.6
Anorexia	1.7	0
Musculoskeletal and Connective Tissue Disorders		
Muscle tightness	1.9	0
Nervous System Disorders		
Headache	22.2	15.6
Dizziness	6.7	5.2
Tremor	2.7	0.5
Paresthesia	1.2	0
Sedation	1.2	0
Tension headache	1.2	0.5
Psychiatric Disorders		
Insomnia	12.3	6.1
Anxiety	8.2	2.4
Initial insomnia	4.3	2.8
Depressed mood	3.9	1.4
Nervousness	3.1	0.5
Restlessness	3.1	0
Agitation	2.2	0.5
Aggression	1.7	0.5
Bruxism	1.7	0.5
Depression	1.7	0.9
Libido decreased	1.7	0.5
Affect lability	1.4	0.9
Confusional state	1.2	0.5
Tension	1.2	0.5
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal pain	1.7	1.4
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	5.1	0.9

* Included doses up to 108 mg.

The majority of ADRs were mild to moderate in severity.

6.2 Other Adverse Reactions Observed in CONCERTA Clinical Trials

This section includes adverse reactions reported by CONCERTA-treated subjects in double-blind trials that do not meet the criteria specified for Table 4 or Table 5 and all adverse reactions reported by CONCERTA-treated subjects who participated in open-label and postmarketing clinical trials.

Blood and Lymphatic System Disorders: Leukopenia

Eye Disorders: Accommodation disorder, Dry eye

Vascular Disorders: Hot flush

Gastrointestinal Disorders: Abdominal discomfort, Abdominal pain, Diarrhea

General Disorders and Administrative Site Conditions: Asthenia, Fatigue, Feeling jittery, Thirst

Infections and Infestations: Sinusitis

Investigations: Alanine aminotransferase increased, Blood pressure increased, Cardiac murmur, Heart rate increased

Musculoskeletal and Connective Tissue Disorders: Muscle spasms

Nervous System Disorders: Lethargy, Psychomotor hyperactivity, Somnolence

Psychiatric Disorders: Anger, Hypervigilance, Mood altered, Mood swings, Panic attack, Sleep disorder, Tearfulness, Tic

Reproductive System and Breast Disorders: Erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea

Skin and Subcutaneous Tissue Disorders: Rash, Rash macular

Vascular Disorders: Hypertension

6.3 Discontinuation Due to Adverse Reactions

Adverse reactions in the 4 placebo-controlled studies of children and adolescents leading to discontinuation occurred in 2 CONCERTA patients (0.6%) including depressed mood (1, 0.3%) and headache and insomnia (1, 0.3%), and 6 placebo patients (1.9%) including headache and insomnia (1, 0.3%), irritability (2, 0.6%), headache (1, 0.3%), psychomotor hyperactivity (1, 0.3%), and tic (1, 0.3%).

In the 2 placebo-controlled studies of adults, 25 CONCERTA patients (6.0%) and 6 placebo patients (2.8%) discontinued due to an adverse reaction. Those events with an incidence of >0.5% in the CONCERTA patients included anxiety (1.7%), irritability (1.4%), blood pressure increased (1.0%), and nervousness (0.7%). In placebo patients, blood pressure increased and depressed mood had an incidence of >0.5% (0.9%).

In the 11 open-label studies of children, adolescents, and adults, 266 CONCERTA patients (7.0%) discontinued due to an adverse reaction. Those events with an incidence of >0.5% included insomnia (1.2%), irritability (0.8%), anxiety (0.7%), decreased appetite (0.7%), and tic (0.6%).

6.4 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.

6.5 Blood Pressure and Heart Rate Increases

In the laboratory classroom clinical trials in children (Studies 1 and 2), both CONCERTA once daily and methylphenidate three times daily increased resting pulse by an average of 2 to 6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1 to 4 mm Hg during the day, relative to placebo. In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with 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. In one placebo-controlled study in adults (Study 6), dose-dependent mean increases of 3.9 to 9.8 bpm from baseline in standing pulse rate were observed with CONCERTA at the end of the double-blind treatment vs. an increase of 2.7 beats/minute with placebo. Mean changes from baseline in standing blood pressure at the end of double-blind treatment ranged from 0.1 to 2.2 mm Hg (systolic) and -0.7 to 2.2 mm Hg (diastolic) for CONCERTA and was 1.1 mm Hg (systolic) and -1.8 mm Hg (diastolic) for placebo. In a second placebo-controlled study in adults (Study 5), mean changes from baseline in resting pulse rate were observed for CONCERTA and placebo at the end of the double-blind treatment (3.6 and –1.6 beats/minute, respectively). Mean changes from baseline in blood pressure at the end of the double–blind treatment for CONCERTA and placebo-treated patients were –1.2 and –0.5 mm Hg (systolic) and 1.1 and 0.4 mm Hg (diastolic), respectively *[see Warnings and Precautions (5.3)]*.

6.6 Postmarketing Experience

The following additional adverse reactions have been identified during postapproval use of CONCERTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency:

Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura

Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystoles, Supraventricular tachycardia, Ventricular extrasystoles

Eye Disorders: Diplopia, Increased intraocular pressure, Mydriasis, Visual impairment

General Disorders: Chest pain, Chest discomfort, Drug effect decreased, Hyperpyrexia, Therapeutic response decreased

Hepatobiliary disorders: Hepatocellular injury, Acute hepatic failure

Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions, and Exanthemas NEC

Investigations: Blood alkaline phosphatase increased, Blood bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal

Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis

Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia, Serotonin syndrome in combination with serotonergic drugs, Motor and Verbal Tics

Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Mania, Logorrhea, Libido changes

Reproductive System and Breast Disorders: Priapism

Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema

Vascular Disorders: Raynaud's phenomenon

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected

adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: *https://sideeffects.health.gov.il*.

7 DRUG INTERACTIONS

7.1 MAO Inhibitors

CONCERTA should not be used in patients being treated (currently or within the preceding 2 weeks) with MAO inhibitors *[see Contraindications (4.3)]*.

7.2 Vasopressor Agents

Because of possible increases in blood pressure, CONCERTA should be used cautiously with vasopressor agents *[see Warnings and Precautions (5.3)]*.

7.3 Coumarin Anticoagulants, Antidepressants, and Selective Serotonin Reuptake Inhibitors

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

7.4 Halogenated Anesthetics

Concomitant use of halogenated anesthetics and CONCERTA may increase the risk of sudden blood pressure and heart rate increase during surgery. Monitor blood pressure and avoid use of CONCERTA in patients being treated with anesthetics on the day of surgery.

7.5 Risperidone

Combined use of methylphenidate with risperidone when there is a change, whether an increase or decrease, in dosage of either or both medications, may increase the risk of extrapyramidal symptoms (EPS). Monitor for signs of EPS.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of CONCERTA on a mg/kg and mg/m^2 basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPAA in pregnant rats was 1-2 times that seen in trials in volunteers and patients with the maximum recommended dose of 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.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

CONCERTA has not been studied in patients greater than 65 years of age.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

CONCERTA contains methylphenidate, a controlled substance.

9.2 Abuse

CONCERTA has a high potential for abuse and misuse which can lead to the development of a substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*. CONCERTA can be diverted for non-medical use into illicit channels or distribution.

Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Misuse is the intentional use, for therapeutic purposes, of a drug by an

individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of methylphenidate may cause increased heart rate, respiratory rate, or blood pressure; sweating; dilated pupils; hyperactivity; restlessness; insomnia; decreased appetite; loss of coordination; tremors; flushed skin; vomiting; and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including CONCERTA, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

In two placebo-controlled human abuse potential studies, single oral doses of CONCERTA were compared to single oral doses of immediate-release methylphenidate (IR MPH) and placebo in subjects with a history of recreational stimulant use to assess relative abuse potential. For the purpose of this assessment, the response for each of the subjective measures was defined as the maximum effect within the first 8 hours after dose administration.

In one study (n=40), both CONCERTA (108 mg) and 60 mg IR MPH compared to placebo produced statistically significantly greater responses on the five subjective measures suggestive of abuse potential. In comparisons between the two active treatments, however, CONCERTA (108 mg) produced variable responses on positive subjective measures that were either statistically indistinguishable from (Abuse Potential, Drug Liking, Amphetamine, and Morphine Benzedrine Group [Euphoria]) or statistically less than (Stimulation – Euphoria) responses produced by 60 mg IR MPH.

In another study (n=49), both doses of CONCERTA (54 mg and 108 mg) and both doses of IR MPH (50 mg and 90 mg) produced statistically significantly greater responses compared to placebo on the two primary scales used in the study (Drug Liking, Euphoria). When doses of CONCERTA (54 mg and 108 mg) were compared to IR MPH (50 mg and 90 mg), respectively, CONCERTA produced statistically significantly lower subjective responses on these two scales than IR MPH. CONCERTA (108 mg) produced responses that were statistically indistinguishable from the responses on these two scales produced by IR MPH (50 mg). Differences in subjective responses to the respective doses should be considered in the context that only 22% of the total amount of methylphenidate in CONCERTA tablets is available for immediate release from the drug overcoat *[see System Components and Performance (11.1)]*.

Although these findings reveal a relatively lower response to CONCERTA on subjective measures suggestive of abuse potential compared to IR MPH at roughly equivalent total MPH doses, the relevance of these findings to the abuse potential of CONCERTA in the community is unknown.

9.3 Dependence

Physical Dependence

CONCERTA may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal signs and symptoms after abrupt discontinuation or dose reduction following prolonged use of CNS stimulants including CONCERTA include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

Tolerance

CONCERTA may produce tolerance. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

10 OVERDOSAGE

10.1 Clinical Effects of Overdose

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

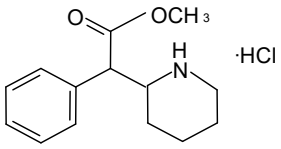
- Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden cardiac death. Takotsubo cardiomyopathy may develop.
- CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin syndrome, seizures, cerebral vascular accidents, and coma may occur.
- Life-threatening hyperthermia (temperatures greater than 104°F) and rhabdomyolysis may develop.

10.2 Overdose Management

Consider the possibility of multiple drug ingestion. The pharmacokinetic profile of CONCERTA should be considered when treating patients with overdose. Because methylphenidate has a large volume of distribution and is rapidly metabolized, dialysis is not useful. Consider contacting the Poison Help line or a medical toxicologist for additional overdose management recommendations.

11 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 α-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:

polyethelene oxide 200K, povidone K29-32, succinic acid, stearic acid, butylated hydroxytoluene (BHT), polyethylene oxide 7000K, sodium chloride, black iron oxide, ferric oxide yellow, ferric oxide red (27mg and 54 mg tablets only), cellulose acetate 398-10, poloxamer 188, hypromellose 2910, 3 cps, phosphoric acid.

Color overcoat:

lactose monohydrate, HPMC, titanium dioxide, triacetin, ferric oxide yellow (18mg and 54 tablets only), stearic acid (18mg tablet only), black iron oxide (27mg tablet only), ferric oxide red (54mg tablet only).

Clear overcoat:

HPMC, polyethylene glycol (macrogol 400), carnauba wax.

Printing ink:

black iron oxide, isopropyl alcohol, propylene glycol, HPMC, purified water.

Each tablet of CONCERTA 18mg contains Lactose monohydrate 6.84mg

Each tablet of CONCERTA 27mg contains Lactose monohydrate 5.20mg

Each tablet of CONCERTA 36mg contains Lactose monohydrate 17.60mg

Each tablet of CONCERTA 54mg contains Lactose monohydrate 8.00mg

11.1 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

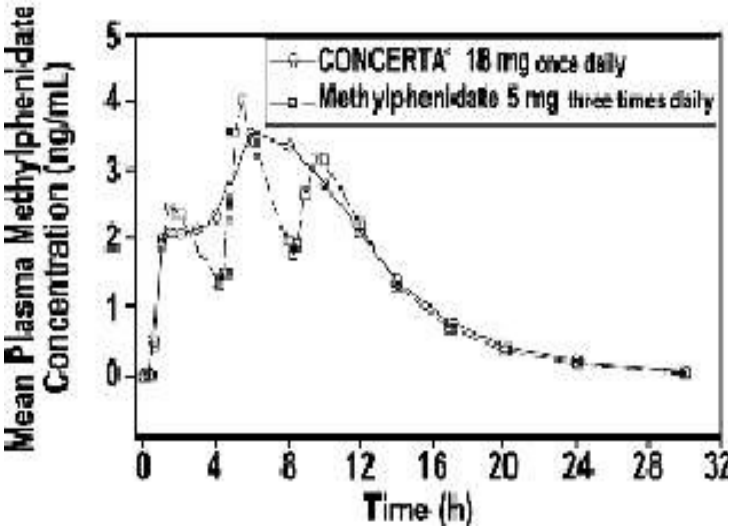
12.3 Pharmacokinetics

Absorption

Methylphenidate is readily absorbed. Following oral administration of 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 and 10 hours.

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

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



The mean single-dose pharmacokinetic parameters in 36 healthy adults following the administration of CONCERTA 18 mg once daily and methylphenidate 5 mg three times daily are summarized in Table 6.

Table 6. Pharmacokinetic Parameters (Mean ± SD) After Single Dose in Healthy Adults

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

The pharmacokinetics of CONCERTA were evaluated in healthy adults following single- and multiple-dose administration (steady state) of doses up to 144 mg/day. The mean half-life was about 3.6 hours. No differences in the pharmacokinetics of 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 in a dose range of 18 to 144 mg.

Dose Proportionality

Following administration of CONCERTA in single doses of 18, 36, and 54 mg/day to healthy

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 1/40 the plasma concentrations of the d-isomer.

In healthy adults, single and multiple dosing of once-daily CONCERTA doses from 54 to 144 mg/day resulted in linear and dose-proportional increases in C_{max} and AUC_{inf} for total methylphenidate (MPH) and its major metabolite, α-phenyl-piperidine acetic acid (PPAA). There was no time dependency in the pharmacokinetics of methylphenidate. The ratio of metabolite (PPAA) to parent drug (MPH) was constant across doses from 54 to 144 mg/day, both after single dose and upon multiple dosing.

In a multiple-dose study in adolescent ADHD patients aged 13 to 16 administered their prescribed dose (18 to 72 mg/day) of 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 hours.

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily by de-esterification to PPAA, which has little or no pharmacologic activity. In adults the metabolism of CONCERTA once daily as evaluated by metabolism to PPAA is similar to that of methylphenidate three times daily. The metabolism of single and repeated once-daily doses of 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 PPAA, accounting for approximately 80% of the dose.

Food Effects

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

Alcohol Effect

An *in vitro* study was conducted to explore the effect of alcohol on the release characteristics of methylphenidate from the CONCERTA 18 mg tablet dosage form. At an alcohol concentration up to 40% there was no increased release of methylphenidate in the first hour. The results with the 18

mg tablet strength are considered representative of the other available tablet strengths.

Special Populations

Gender

In healthy adults, the mean dose-adjusted AUC $_{(0\text{-inf})}$ 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 have 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 PPAA. 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of 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.

Mutagenesis

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

Impairment of Fertility

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

14 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 and 2 double-blind placebo-controlled studies in adults who met the Diagnostic and Statistical Manual 4^{th} edition (DSM-IV) criteria for ADHD.

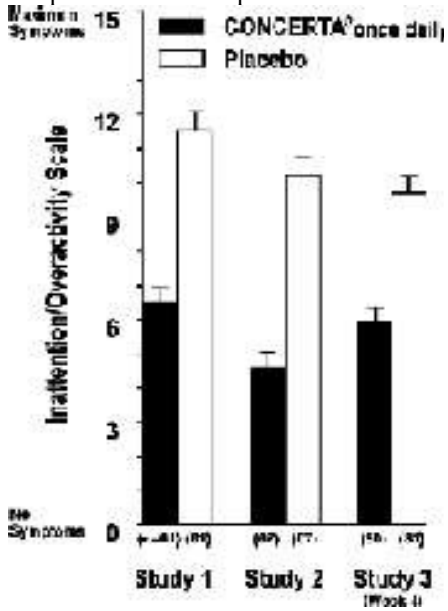
14.1 Children

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

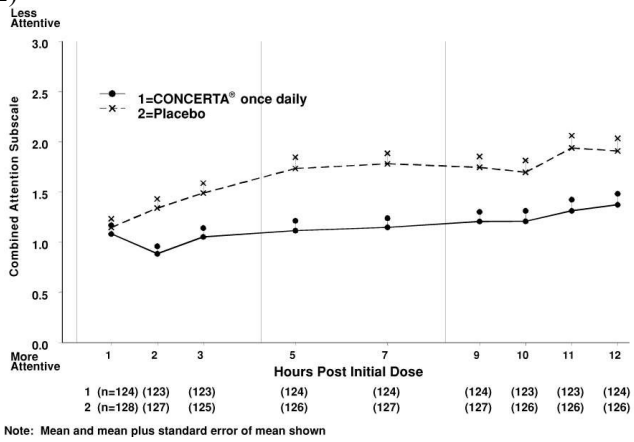
Figure 2. Mean Community School Teacher IOWA Conners Inattention/Overactivity Scores with CONCERTA once daily (18, 36, or 54 mg) and placebo. Studies 1 and 2 involved a 3-way crossover of 1 week per treatment arm. Study 3 involved 4 weeks of parallel-group treatments with a Last Observation Carried Forward 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 statistically 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. Laboratory School Teacher SKAMP Ratings: Mean (SEM) of Combined Attention (Studies 1 and 2)



14.2 Adolescents

In a randomized, double-blind, multicenter, placebo-controlled trial (Study 4) involving 177 patients, CONCERTA was demonstrated to be effective in the treatment of ADHD in adolescents aged 13 to 18 years at doses up to 72 mg/day (1.4 mg/kg/day). Of 220 patients who entered an open 4-week titration phase, 177 were titrated to an individualized dose (maximum of 72 mg/day) based on meeting specific improvement criteria on the ADHD Rating Scale and the Global Assessment of Effectiveness with acceptable tolerability. Patients who met these criteria were then randomized to receive either their individualized dose of 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 statistically significantly superior to placebo.

14.3 Adults

Two double-blind, placebo-controlled studies were conducted in 627 adults aged 18 to 65 years. The controlled studies compared CONCERTA administered once daily and placebo in a multicenter, parallel-group, 7-week dose-titration study (Study 5) (36 to 108 mg/day) and in a multicenter, parallel-group, 5-week, fixed-dose study (Study 6) (18, 36, and 72 mg/day).

Study 5 demonstrated the effectiveness of CONCERTA in the treatment of ADHD in adults aged 18 to 65 years at doses from 36 mg/day to 108 mg/day based on the change from baseline to final study visit on the Adult ADHD Investigator Rating Scale (AISRS). Of 226 patients who entered the 7-week trial, 110 were randomized to CONCERTA and 116 were randomized to placebo. Treatment was initiated at 36 mg/day and patients continued with incremental increases of 18 mg/day (36 to 108 mg/day) based on meeting specific improvement criteria with acceptable tolerability. At the final study visit, mean change scores (LS Mean, SEM) for the investigator rating on the AISRS demonstrated that CONCERTA was statistically significantly superior to placebo.

Study 6 was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-response study (5-week duration) with 3 fixed-dose groups (18, 36, and 72 mg). Patients were randomized to receive CONCERTA administered at doses of 18 mg (n=101), 36 mg (n=102), 72 mg/day (n=102), or placebo (n=96). All three doses of CONCERTA were statistically significantly more effective than placebo in improving CAARS (Conners' Adult ADHD Rating Scale) total scores at double-blind end point in adult subjects with ADHD.

15 HOW SUPPLIED/STORAGE AND HANDLING

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 30 tablets.

18 mg	30-count bottle
27 mg	30-count bottle
36 mg	30-count bottle
54 mg	30-count bottle

Storage and Handling

Store below 25°C. Keep the bottle tightly closed. Keep out of the sight and reach of children.

Shelf life

The expiry date of the product is indicated on the packaging materials.

16 REGISTRATION HOLDER

J-C Heath Care Ltd., Kibbutz Shefayim, 6099000, Israel.

17 MANUFACTURER

Janssen-Cilag Manufacturing L.L.C., State Road 933 km 0.1 Namey Ward, Gurabo, Puerto Rico (PR) 0078, USA.

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