PRODUCT NAME
CONCERTA®

FOR SPECIALIST'S USE ONLY

DOSAGE FORMS AND STRENGTHS
Extended-release tablets

18 mg tablet
Capsule-shaped yellow tablet with "alza 18" printed on one side in black ink. Each tablet contains 18 mg of methylphenidate hydrochloride.

27 mg tablet
Capsule-shaped gray tablet with "alza 27" printed on one side in black ink. Each tablet contains 27 mg of methylphenidate hydrochloride.

36 mg tablet
Capsule-shaped white tablet with "alza 36" printed on one side in black ink. Each tablet contains 36 mg of methylphenidate hydrochloride.

For excipients, see *List of Excipients*

CLINICAL INFORMATION
Indications
CONCERTA is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of CONCERTA in the treatment of ADHD was established in controlled trials of children and adolescents aged 6 to 17 and adults aged 18 to 65 who met DSM-IV criteria for ADHD.

CONCERTA should be used as a part of a comprehensive treatment program where remedial measures alone prove insufficient. A comprehensive treatment program for the treatment of ADHD may include other measures (psychological, educational, social) for patients with this disorder. Diagnosis must be made according to the current DSM criteria or ICD guidelines.

CONCERTA treatment is not indicated in all patients with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity of the patient's symptoms. Stimulants are not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential, and psychosocial intervention is often helpful.

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.

Dosage and Administration

Dosage

Patients new to methylphenidate

The recommended starting dosage 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.

Patients currently using methylphenidate

The recommended dosage of CONCERTA for patients who are currently taking methylphenidate twice daily or three times daily, at dosages of 10 to 60 mg/day, is provided in the following table:

Recommended Dosage Conversion from Methylphenidate Regimens to CONCERTA

Previous Methylphenidate Daily Dose	Recommended CONCERTA Starting Dosage
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

Clinical judgment should be used when selecting the dose for patients currently taking methylphenidate in other regimens.

Dose titration

The dosage should be individualized according to the needs and responses of the patient. Doses may be increased in 18 mg increments at weekly intervals. The maximum daily dosage of CONCERTA is 54 mg in children and 72 mg in adolescents and adults.

Maintenance/extended treatment

The long-term use of methylphenidate 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.

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.

Special populations

Pediatrics (under 6 years of age)

Use of CONCERTA in patients under six years of age has not been studied in controlled trials. CONCERTA should not be used in patients under six years old.

***Elderly (over 65 years of age*)**
Use of CONCERTA in elderly patients over 65 years of age has not been studied in controlled trials.

Renal insufficiency
There is no experience with the use of CONCERTA in patients with renal insufficiency (see *Pharmacokinetic Properties - Special populations, Renal insufficiency).*

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

Administration
CONCERTA is administered orally once daily. As the effect has been shown to be present 12 hours after dosing, the product should be taken once daily in the morning.

CONCERTA must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed (see *Warnings and Precautions - Dose administration*).

CONCERTA may be administered with or without food (see *Pharmacokinetic Properties - Food effects*).

Contraindications
CONCERTA is contraindicated:

- in patients known to be hypersensitive to methylphenidate or other components of the product;
- 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 *Interactions).*

Warnings and Precautions
Structural cardiac abnormalities
Although a causal relationship has not been established, sudden death has been reported in patients with structural cardiac abnormalities treated with ADHD drugs with stimulant effects. These treatments should be used with caution in patients with structural cardiac abnormalities.

Patients under six years old
CONCERTA should not be used in patients under six years old. Sufficient data on the safety of long-term use of methylphenidate is not yet available.

Motor and verbal tics, and worsening of Tourette's syndrome
Central nervous system (CNS) stimulants, including methylphenidate, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. It is recommended that the family history be assessed, and that the patient is clinically evaluated for tics or Tourette's syndrome

before initiating methylphenidate. Regular monitoring for the emergence or worsening of tics or Tourette's syndrome during treatment with methylphenidate is recommended at every dose adjustment and every visit, and treatment discontinued if clinically appropriate.

Long-term use
Although a causal relationship has not been established, suppression of growth (i.e., weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted.

Increased Intraocular Pressure and Glaucoma
There have been reports of an elevation of intraocular pressure (IOP) associated with methylphenidate treatment.

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.

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.

Dose administration
CONCERTA must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a non-absorbable 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.

Because the CONCERTA tablet is non-deformable and does not appreciably change in shape in the GI tract, CONCERTA should ordinarily not be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in non-deformable 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.

Use in other indications
CONCERTA should not be used to treat severe depression and/or for the prevention or treatment of normal fatigue states.

Psychotic or manic symptoms
Psychotic (e.g., hallucinations) or manic symptoms have been reported in patients without a prior history of psychotic illness or mania during treatment with CONCERTA at usual doses. If such symptoms occur, consideration should be given to a possible causal role of CONCERTA and discontinuation of treatment may be appropriate (see *Adverse Reactions*).

Aggression, anxiety and agitation
Aggressive behavior, marked anxiety, or agitation are often observed in patients with ADHD, and have been reported in patients treated with CONCERTA (see Adverse Reactions). Anxiety led to discontinuation of CONCERTA in some patients. It is recommended to monitor patients beginning treatment with CONCERTA for the appearance of, or worsening of, aggressive behavior, marked anxiety, or agitation.

Priapism
Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Cerebrovascular disorders
Cerebrovascular disorders (including cerebral vasculitis and cerebral hemorrhage) have been reported with the use of CONCERTA (see Adverse Reactions). Consider cerebrovascular disorders as a possible diagnosis in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during CONCERTA therapy. These symptoms could include severe headache, unilateral weakness or paralysis, and impairment of coordination, vision, speech, language, or memory. If a cerebrovascular disorder is suspected during treatment, discontinue CONCERTA immediately. Early diagnosis may guide subsequent treatment.

In patients with pre-existing cerebrovascular disorders (e.g., aneurysm, vascular malformations/anomalies), treatment with CONCERTA is not recommended.

Conditions requiring caution
CONCERTA should be given with caution in the following conditions:

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

Underlying medical conditions that might be compromised by increases in blood pressure or heart rate: In the laboratory classroom clinical trials in children, both CONCERTA 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 placebo-

controlled studies in adults, mean increases in resting pulse rate of approximately 4 to 6 bpm were observed with CONCERTA at endpoint vs. a mean change of roughly –2 to 3 bpm with placebo. Mean changes in blood pressure at endpoint ranged from about –1 to 1 mm Hg (systolic) and 0 to 1 mm Hg (diastolic) for CONCERTA and from -1 to 1 mm Hg (systolic) and –2 to 0 mm Hg (diastolic) for placebo. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. Blood pressure (especially for patients with hypertension) and heart rate should be monitored at appropriate intervals in patients taking CONCERTA.

History of drug dependence or alcoholism: 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.

Hematologic monitoring
Periodic hematologic monitoring (Complete Blood Count, differential, and platelet counts) is advised during prolonged therapy.

Interactions

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

Because of possible increases in blood pressure, CONCERTA should be used cautiously with vasopressor agents.

CONCERTA may decrease the effectiveness of drugs used to treat hypertension. It is recommended to monitor blood pressure and adjust the dosage of the antihypertensive drug as needed (see *Warnings and Precautions – Underlying medical conditions that might be compromised by increases in blood pressure or heart rate*).

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

There have been reports of serotonin syndrome following coadministration of methylphenidate with serotonergic drugs. If concomitant use of CONCERTA with a serotonergic drug is warranted, prompt recognition of the symptoms of serotonin syndrome is important. CONCERTA must be discontinued as soon as possible if serotonin syndrome is suspected.

Because a predominant action of methylphenidate is to increase extracellular dopamine levels, CONCERTA may be associated with pharmacodynamic interactions when co-administered with some antipsychotics. Caution is warranted in patients receiving both CONCERTA and an antipsychotic, as extrapyramidal symptoms could emerge when

these drugs are administered concomitantly or when adjusting the dosage of one or both drugs.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., 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.

Pregnancy, Breast-feeding and Fertility

Pregnancy

The safety of methylphenidate for use during human pregnancy has not been established. No studies are available on the use of CONCERTA in pregnant women. CONCERTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Methylphenidate hydrochloride 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.

Teratogenic effects were not seen in rats at methylphenidate hydrochloride doses up to 30 mg/kg/day, resulting in a systemic exposure to methylphenidate of approximately seven times that seen in trials in adult and adolescent volunteers and patients receiving daily dose of 72mg of CONCERTA, based on pharmacokinetic data.

Breast-feeding

Methylphenidate has been detected in human milk. Based on breast milk sampling from five mothers, methylphenidate concentrations in human milk resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage, and a milk to maternal plasma ratio ranging between 1.1 and 2.7. Caution should be exercised if CONCERTA is administered to a breast-feeding woman.

Fertility

Methylphenidate did not impair fertility in mice that received up to 160 mg/kg/day methylphenidate hydrochloride in an 18-week Continuous Breeding study.

Effects on Ability to Drive and Use Machines

Stimulants may impair the ability of the patient to operate potentially hazardous machinery or vehicles. Patients should be cautioned accordingly until they are reasonably certain that CONCERTA does not adversely affect their ability to engage in such activities.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of methylphenidate hydrochloride based on the comprehensive assessment of the available adverse event information. A causal relationship with methylphenidate

hydrochloride 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 the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

Double-blind data – adverse reactions reported at ≥1% frequency

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

Pediatric patients

The safety of CONCERTA was evaluated in 639 pediatric patients (children and adolescents) with ADHD who participated in 4 placebo-controlled, double-blind clinical trials. The information presented in this section was derived from pooled data.

Adverse reactions reported by ≥1% of CONCERTA-treated children and adolescent patients in these trials are shown in Table 1.

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

System/Organ Class Adverse Reaction	**CONCERTA (n=321) %**	**Placebo (n=318) %**
Infections and Infestations		
Nasopharyngitis	2.8	2.2
Psychiatric Disorders		
Insomnia*	2.8	0.3
Nervous System Disorders		
Dizziness	1.9	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1.9	0.9
Oropharyngeal Pain	1.2	0.9
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

*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.

Adult patients

The safety of CONCERTA was evaluated in 905 adult patients with ADHD who participated in 3 placebo-controlled, double-blind clinical trials. The information presented in this section was derived from pooled data.

Adverse reactions reported by ≥1% of CONCERTA-treated adult patients in these trials are shown in Table 2.

Table 2. Adverse Reactions Reported by ≥1% of CONCERTA-Treated Adult Patients in 3 Placebo-Controlled, Double-Blind Clinical Trials

System/Organ Class Adverse Reaction	CONCERTA (n=596) %	Placebo (n=309) %
Infections and Infestations		
Upper respiratory tract infection	1.7	1.0
Sinusitis	1.3	1.0
Metabolism and Nutrition Disorders		
Decreased appetite	24.8	6.1
Anorexia	4.2	1.3
Psychiatric Disorders		
Insomnia	13.3	7.8
Anxiety	8.4	2.9
Initial insomnia	5.7	2.6
Depressed mood	4.4	2.6
Restlessness	4.0	0
Agitation	3.2	0.6
Nervousness	2.3	0.6
Bruxism	1.5	0.6
Depression	1.5	0.6
Affect lability	1.3	0.6
Libido decreased*	1.5	0.6
Panic attack	1.3	0.3
Tension	1.3	0.3
Aggression	1.2	0.6
Confusional state	1.0	0.3
Nervous System Disorders		
Headache	24.2	18.8
Dizziness	7.4	5.5
Tremor	3.4	0.6
Paresthesia	1.2	0
Tension headache	1.0	0.3
Eye Disorders		
Accommodation disorder	1.3	0
Vision blurred	1.3	1.0
Ear and Labyrinth Disorders		
Vertigo	2.0	0.3
Cardiac Disorders		
Tachycardia	6.0	0
Palpitations	4.5	0.6
Vascular Disorders		
Hypertension	2.2	1.6
Hot flush	1.3	0.6
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal pain	1.5	1.3
Cough	1.2	1.0
Dyspnea	1.2	0.6
Gastrointestinal Disorders		
Dry mouth	15.1	3.6
Nausea	14.3	4.9
Dyspepsia	2.0	1.9
Vomiting	1.8	0.6

Table 2. Adverse Reactions Reported by ≥1% of CONCERTA-Treated Adult Patients in 3 Placebo-Controlled, Double-Blind Clinical Trials		
System/Organ Class Adverse Reaction	**CONCERTA (n=596)** %	**Placebo (n=309)** %
Constipation	1.5	0.6
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	5.7	1.3
Musculoskeletal and Connective Tissue Disorders		
Muscle tightness	1.3	0
Muscle spasms	1.0	0.3
Reproductive System and Breast Disorders		
Erectile dysfunction	1.0	0.3
General Disorders and Administration Site Conditions		
Irritability	5.2	2.9
Fatigue	4.7	4.2
Thirst	1.8	0.6
Asthenia	1.2	0
Investigations		
Weight decreased	8.7	3.6
Heart rate increased	3.0	1.9
Blood pressure increased	2.5	1.9
Alanine aminotransferase increased	1.0	0

* The adverse reaction Libido decreased includes the preferred term Loss of libido

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

Open-label data - adverse reactions reported at ≥1% frequency

The safety of CONCERTA was evaluated in 3782 pediatric and adult patients with ADHD who participated in 12 open-label clinical trials. The information presented in this section was derived from pooled data.

Adverse reactions reported by ≥1% of CONCERTA-treated patients in these trials and not listed in Table 1 and 2 are shown in Table 3.

Table 3. Adverse Reactions Reported by ≥1% of CONCERTA-Treated Patients in 12 Open-Label Clinical Trials	
System/Organ Class Adverse Reaction	**CONCERTA (n=3782)** **%**
Psychiatric Disorders	
Tic	2.0
Mood swings	1.1
Nervous System Disorders	
Somnolence	1.0
Gastrointestinal Disorders	
Diarrhea	2.4
Abdominal discomfort	1.3
Abdominal pain	1.2
Skin and Subcutaneous Tissue Disorders	
Rash	1.3
General Disorders and Administration Site Conditions	
Feeling jittery	1.4

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

Double blind and open-label data - adverse reactions reported at <1% frequency
Additional adverse reactions that occurred in <1% of CONCERTA-treated pediatric and adult patients in the double-blind and open-label clinical datasets are listed in Table 4.

Table 4. Adverse Reactions Reported by <1% of CONCERTA-Treated Pediatric and Adult Patients in Either Double-Blind or Open-Label Clinical Trials
System/Organ Class Adverse Reaction
Blood and Lymphatic System Disorders
Leukopenia
Psychiatric Disorders
Anger, Sleep disorder, Hypervigilance, Tearfulness, Mood altered
Nervous System Disorders
Psychomotor hyperactivity, Sedation, Lethargy
Eye Disorders
Dry eye
Skin and Subcutaneous Tissue Disorders
Rash macular
Investigations
Cardiac murmur

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

Postmarketing data
Adverse reactions identified during postmarketing experience with CONCERTA are included in Table 5. In this table, the frequencies are provided according to the following convention:

Very common	≥ 1/10 (≥10%)
Common	≥ 1/100 to < 1/10 (≥1% and <10%)
Uncommon	≥ 1/1,000 to < 1/100 (≥0.1% and <1%)
Rare	≥ 1/10,000 to < 1/1,000 (≥0.01 and <0.1%)
Very rare	< 1/10,000 (<0.01%), including isolated reports
Not known	Cannot be estimated from the available data

Table 5. Adverse Reactions Identified During Postmarketing Experience with CONCERTA	
System Organ Class Adverse Reaction	**Frequency Category Estimated from Spontaneous Reporting Rates**
Blood and Lymphatic System Disorders	
Pancytopenia	Very rare
Thrombocytopenia	Very rare
Thrombocytopenic purpura	Very rare
Immune System Disorders	
Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions and Exanthemas NEC	Rare

Table 5. Adverse Reactions Identified During Postmarketing Experience with CONCERTA	
System Organ Class Adverse Reaction	**Frequency Category Estimated from Spontaneous Reporting Rates**
Psychiatric Disorders	
Disorientation	Very rare
Hallucination	Very rare
Hallucination auditory	Very rare
Hallucination visual	Very rare
Mania	Very rare
Logorrhea	Very rare
Libido disorder*	Very rare
Obsessive-compulsive disorders and symptoms (including trichotillomania, obsessive thoughts, compulsions)	Very rare
Nervous System Disorders	
Convulsion	Very rare
Grand mal convulsion	Very rare
Cerebrovascular disorder (including cerebral vasculitis, cerebral hemorrhage, cerebral arteritis, cerebral vascular occlusion)	Very rare
Dyskinesia	Very rare
Eye Disorders	
Diplopia	Very rare
Mydriasis	Very rare
Visual impairment	Very rare
Cardiac Disorders	
Angina pectoris	Very rare
Bradycardia	Very rare
Extrasystoles	Very rare
Supraventricular tachycardia	Very rare
Ventricular extrasystoles	Very rare
Vascular Disorders	
Raynaud's phenomenon	Very rare
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Very rare
Hepatobiliary Disorders	
Blood alkaline phosphatase increased	Very rare
Blood bilirubin increased	Very rare
Hepatic enzyme increased	Very rare
Hepatocellular injury	Very rare
Acute hepatic failure	Very rare
Skin and Subcutaneous Tissue Disorders	
Alopecia	Very rare
Erythema	Very rare
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	Very rare
Myalgia	Very rare
Muscle twitching	Very rare
Reproductive System and Breast Disorders	
Priapism	Very rare
Gynecomastia	Very rare

Table 5. Adverse Reactions Identified During Postmarketing Experience with CONCERTA	
System Organ Class Adverse Reaction	**Frequency Category Estimated from Spontaneous Reporting Rates**
General Disorders and Administration Site Conditions	
Therapeutic response decreased	Rare
Chest pain	Very rare
Chest discomfort	Very rare
Drug effect decreased	Very rare
Hyperpyrexia	Very rare
Investigations	
Platelet count decreased	Very rare
White blood cell count abnormal	Very rare

NEC Not elsewhere classified

* The adverse reaction Libido disorder includes terms apart from those associated with decreases in libido

Overdose

Symptoms and signs

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

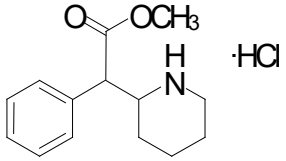
Treatment

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. The efficacy of activated charcoal has not been established. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for pyrexia.

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

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

PHARMACOLOGICAL PROPERTIES



Pharmacodynamic Properties
Pharmacotherapeutic group: centrally acting sympathomimetics, ATC code: N06BA04.

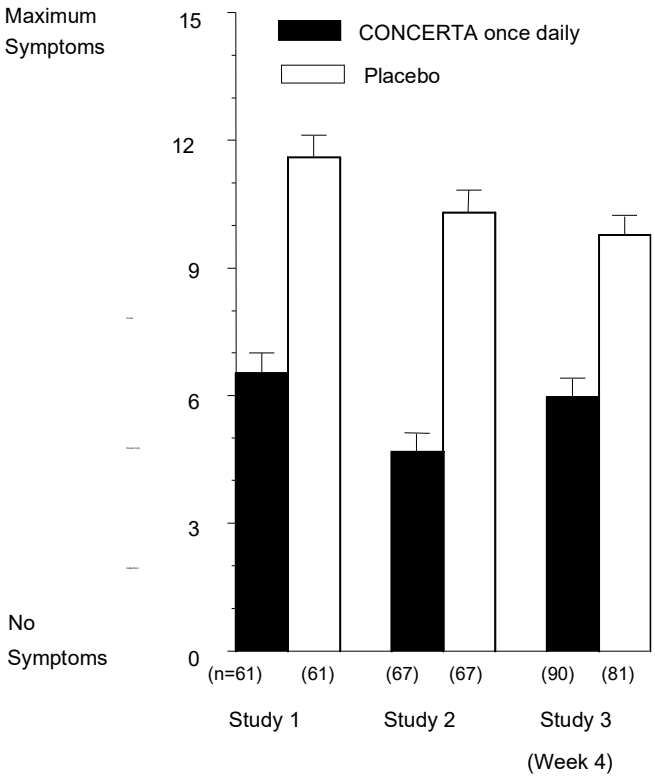
Mechanism of action
Methylphenidate hydrochloride is a CNS stimulant. The mode of therapeutic action in ADHD is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

Clinical Studies
CONCERTA was demonstrated to be effective in the treatment of 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 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 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.

In Studies 1, 2 and 3, 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 1.

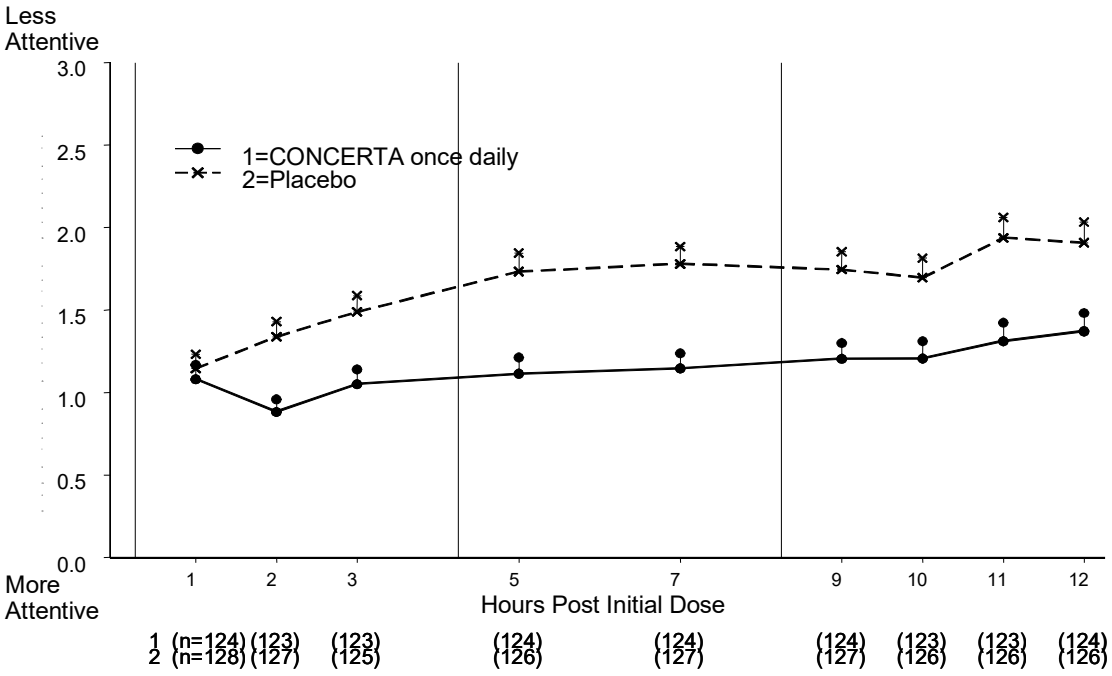
Figure 1. Mean Community School Teacher IOWA Conners Inattention/Overactivity Scores with CONCERTA



Error bars represent the mean plus standard error of the mean
Study 3 - Last Observation Carried Forward analysis was at week 4

In Studies 1 and 2, symptoms of ADHD were evaluated by laboratory schoolteachers using the SKAMP (Swanson, Kotkin, Agler, M-Flynn, and Pelham) 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 2 presents the laboratory schoolteacher SKAMP ratings for CONCERTA and placebo.

Figure 2. Laboratory School Teacher SKAMP Ratings: Mean (SEM) of Combined-Attention Score (Studies 1 and 2)



Note: Mean and mean plus standard error of mean shown

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.

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.

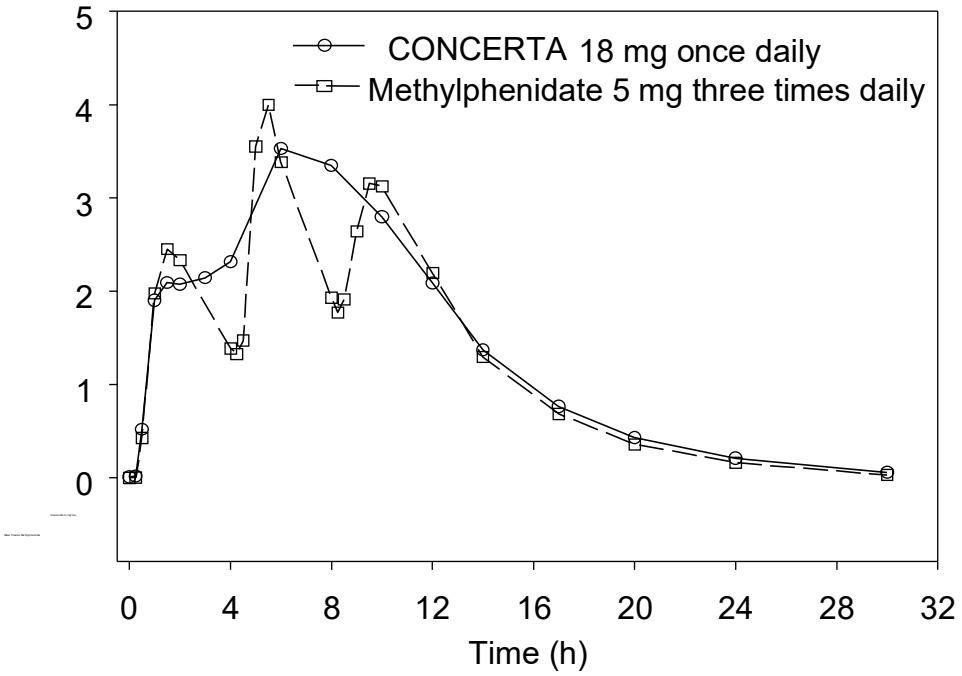
Study 6 was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-response study (5-week duration) with 3 fixed-dose groups (18, 36, and 72 mg). Patients were randomized to receive CONCERTA administered at doses of 18 mg (n=101), 36 mg (n=102), 72 mg/day (n=102), or placebo (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.

Pharmacokinetic Properties

Absorption

Methylphenidate is readily absorbed. Following oral administration of CONCERTA to adults, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 to 2 hours, then increase gradually over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours after which a gradual decrease in plasma levels of methylphenidate begins. CONCERTA once daily minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily – see mean plasma concentration versus time profiles in Figure 3. The relative bioavailability of CONCERTA once daily and methylphenidate three times daily in adults is comparable.

Figure 3. 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 pharmacokinetic parameters in 36 adults following the administration of CONCERTA 18 mg once daily and methylphenidate hydrochloride 5 mg three times daily are summarized in Table 6.

Table 6 Mean ± SD Pharmacokinetic Parameters

PARAMETERS	CONCERTA (18 mg once daily) (n = 36)	Methylphenidate hydrochloride (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
$t_{1/2}$ (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 ½ following repeated once daily dosing are similar to those following the first dose of CONCERTA.

Dose proportionality

Following administration of CONCERTA in single doses of 18, 36, and 54 mg/day to healthy adults, C_{max} and AUC_{inf} of d-methylphenidate were proportional to dose, whereas l-methylphenidate C_{max} and AUC_{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 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, (alpha)-phenyl-piperidine acetic acid (PPAA). The single dose and steady state (Day 4) clearance and half-life parameters were similar, indicating that 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 years administered 18 to 72 mg/day of CONCERTA, mean C_{max} and AUC during a dosing interval of the d-isomer and total methylphenidate increased proportionally with respect to dose.

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

Metabolism
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.

Elimination
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_{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_{inf} was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age
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 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.

NON-CLINICAL INFORMATION
In a lifetime carcinogenicity study carried out in mice, methylphenidate hydrochloride 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 is considerably higher than the recommended human dose on a mg/kg basis. 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.

A similar lifetime study in the rat at a methylphenidate hydrochloride dose of up to 45 mg/kg/day showed no evidence of carcinogenicity.

In a 24-week study in the transgenic mouse strain p53+/-, there was no evidence of carcinogenicity at methylphenidate hydrochloride doses of up to 74 mg/kg/day.

No adverse toxicologic effects were seen in two separate 30-day oral dosing studies in dogs with CONCERTA at doses up to 72 mg/day (up to 8.6 mg/kg/day) and 144 mg/day (up to 22 mg/kg/day), respectively.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchange and chromosome aberrations were increased in an *in vitro* test on cultured ovary cells of Chinese Hamster. Methylphenidate was negative *in vivo* in the mouse bone marrow micronucleus assay.

All other safety data relevant to the prescriber have been included in the appropriate section.

PHARMACEUTICAL INFORMATION

List of Excipients

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
Triacetin.

Incompatibilities

Not known.

Shelf Life

24 months

Storage Conditions

Store below 30°C. Keep the container tightly closed.
Keep out of the reach of children.

Nature and Contents of Container

CONCERTA is available in high-density polyethylene (HDPE) bottles. Each HDPE bottle contains 30 tablets and desiccant.

Instructions for Use/Handling

No special requirements

MANUFACTURER

Janssen Cilag Manufacturing, L.L.C
State Road 933, KM 0.1, Mamey Ward, Gurabo, Puerto Rico (PR)
00778, United States (USA)

PRODUCT REGISTRATION HOLDER

Johnson & Johnson Sdn Bhd (3718-D)
Level 8, The Pinnacle,
Persiaran Lagoon, Bandar Sunway,
46150, Petaling Jaya, Selangor, Malaysia

DATE OF REVISION OF THE TEXT

16 August 2024 (CCDS v19Mar2024 + Canada PI v31May2023 + US PI v13Oct2023)