PRODUCT MONOGRAPH

CONCERTA®

methylphenidate hydrochloride

Extended-release Tablets

18 mg, 27 mg, 36 mg, and 54 mg

House Standard

CNS Stimulant

Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9

Distribution Address:
Markham, Ontario
L3R 0T5

www.janssen.com/canada

Date of Preparation:
June 18, 2003

Date of Revision:
April 17, 2019

Submission Control No: 224296

An ALZA OROS® Technology Product

Table of Contents

CONCERTA®

methylphenidate hydrochloride

Extended-release Tablets

18 mg, 27 mg, 36 mg, and 54 mg

House Standard

CNS Stimulant

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	Extended-release tablet 18 mg, 27 mg, 36 mg, and 54 mg	Butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide and triacetin

INDICATIONS AND CLINICAL USE

CONCERTA® (methylphenidate hydrochloride) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in:

- **Children (6 – 12 years of age)**
- **Adolescents (13 – 18 years of age)**
- **Adults (> 18 years of age)**

Pediatrics (< 6 years of age):
CONCERTA® should not be used in children under six years, since safety and efficacy in this age group have not been established.

Geriatrics (> 65 years of age):
No data available.
A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and that were present before age 7 years. The symptoms must be persistent, must be more severe than is typically observed in individuals at a comparable level of development, must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and must be present in 2 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 6 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 6 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. For a Combined Type diagnosis, both inattentive and hyperactive-impulsive criteria must be met.

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

Need for Comprehensive Treatment Program
CONCERTA® is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Drug treatment is 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 in children and adolescents with this diagnosis and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Long-Term Use
The effectiveness of CONCERTA® for long-term use, i.e., for more than 4 weeks in children and adolescents or 7 weeks in adults, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use CONCERTA® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

- Thyrotoxicosis, advanced arteriosclerosis, symptomatic cardiovascular disease or moderate to severe hypertension or glaucoma.
- Patients who are hypersensitive to methylphenidate or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- During treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result) (see **DRUG INTERACTIONS; Drug-Drug Interactions**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Drug Dependence** (see **Dependence/Tolerance** section below)

General

CONCERTA® is intended for oral use only. In dogs, the intravenous injection of the pulverized CONCERTA® tablets resulted in death (see ***Product Monograph Part II*: TOXICOLOGY, Acute Toxicity**).

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with stimulant drugs used for ADHD treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious cardiac problems. Although some serious heart problems alone carry an increased risk of sudden death, CONCERTA® generally should not be used in children, adolescents, or adults with known 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 (see **CONTRAINDICATIONS**).

General

Children: Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for sudden/cardiac death arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: a) are involved in strenuous exercise or activities, b) use other sympathomimetic ADHD drugs or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment with sympathomimetic medications, a personal and family history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during ADHD treatment should undergo a prompt cardiac evaluation.

Fatigue

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

Information for Patients

Patients should be informed that CONCERTA® should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a 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. Patient information is provided in ***Product Monograph Part III*: CONSUMER INFORMATION**. To assure safe and effective use of CONCERTA®, the information and instructions provided in ***Product Monograph Part III*: CONSUMER INFORMATION** should be discussed with patients.

Carcinogenesis and Mutagenesis

See ***Product Monograph Part II*: TOXICOLOGY; Carcinogenicity and Mutagenicity** and **Reproductive and Developmental Toxicity** for discussion on animal data.

Cardiovascular

Pre-Existing Cardiovascular and Cerebral Vascular Conditions

CNS stimulants should be used with caution in patients with a pre-existing cardiovascular or cerebrovascular condition, taking into account risk predictors for these conditions. Patients should be screened for pre-existing or underlying cardiovascular or cerebrovascular conditions before initiation of treatment with CONCERTA® and monitored for new conditions of the heart or brain during the course of treatment.

Hypertension and Other Cardiovascular Conditions

CONCERTA® should be used cautiously in patients with mild hypertension and other cardiovascular conditions. Blood pressure should be monitored at appropriate intervals in patients receiving CONCERTA®, especially in patients with hypertension. In the laboratory

classroom clinical trials in children (Studies 1 and 2), both CONCERTA® and methylphenidate t.i.d. increased resting pulse by an average of 2-6 beats per minute (bpm) and produced average increases of systolic blood pressure (SBP) and diastolic blood pressure (DBP) of approximately 1-4 mm Hg during the day, relative to placebo. In the double-blind, placebo-controlled study in adults (Study 5), changes in mean DBP and SBP were observed with CONCERTA® doses up to 72 mg. A statistically significant ($p<0.05$) mean increase in standing DBP and SBP versus baseline was reached at Week 1 in the 72 mg CONCERTA® dose group (mean increase of 2.0 mm Hg for standing DBP and 4.0 mm Hg for standing and supine SBP) but not at later time points. A statistically significant increase in pulse was observed for all CONCERTA® dose groups (18 mg, 36 mg and 72 mg) versus baseline (range of mean increase of 2.0-10.6 bpm). Therefore, caution is advised in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure or recent myocardial infarction.

Dependence/Tolerance

Drug Dependence

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

Endocrine and Metabolism

Long-Term Suppression of Growth

Sufficient data on the safety of long-term use of methylphenidate in children are not yet available. 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.

Gastrointestinal

Potential for Gastrointestinal Obstruction

Because the CONCERTA® tablet does not appreciably change in shape in the gastrointestinal tract, CONCERTA® should not be administered to patients with pre-existing gastrointestinal narrowing (pathologic or iatrogenic, such as 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 other drugs in nondeformable controlled-release formulations. There have been very rare reports of obstructive symptoms associated with the use of CONCERTA® in patients without known gastrointestinal stricture. Due to the controlled-release design, CONCERTA® tablets should only be used in patients who are able to swallow the tablets whole (see **DOSAGE AND ADMINISTRATION, Administration**).

Neurologic

Cerebrovascular disorders

Cerebrovascular disorders (including cerebral vasculitis and cerebral hemorrhage) have been reported with the use of CONCERTA®. 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 (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

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

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 (see **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions,** Adverse Reactions Occurring in Long-Term Safety Trials).

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.

Ophthalmologic

Increased intraocular pressure and glaucoma

There have been reports of elevation of intraocular pressure (IOP) and glaucoma associated with methylphenidate treatment. CONCERTA® is contraindicated in patients with glaucoma (see **CONTRAINDICATIONS**).

Psychiatric

Pre-Existing Psychosis

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

Screening Patients for Bipolar Disorder

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of

suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms
Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania, can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression, Anxiety and Agitation
Aggressive behaviour, marked anxiety or agitation are often observed in patients with ADHD, and haves been reported in patients treated with CONCERTA® (see **ADVERSE REACTIONS, Clinical Trial Adverse Drug 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 behaviour, marked anxiety or agitation, in which case consider discontinuing methylphenidate.

Suicidal Behaviour and Ideation
There have been post-marketing reports of suicide-related events in patients treated with ADHD drugs, including cases of ideation, attempts, and very rarely, completed suicide. The mechanism of this risk is not known. ADHD and its related co-morbidities may be associated with increased risk of suicidal ideation and/or behaviour.

Therefore, it is recommended for patients treated with ADHD drugs that caregivers and physicians monitor for signs of suicide-related behaviour, including at dose initiation/optimization and drug discontinuation. Patients should be encouraged to report any distressing thoughts or feelings at any time to their healthcare professional. Patients with emergent suicidal ideation and behaviour should be evaluated immediately. The physician should initiate appropriate treatment of the underlying psychiatric condition and consider a possible change in the ADHD treatment regimen (see **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**).

Serotonin Syndrome
Serotonin syndrome is a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Serotonin syndrome has been reported when methylphenidate was co-administered with serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Other common serotonergic drugs include: tricyclic antidepressants (TCAs), serotonin 5-HT1 receptor agonists (triptans), and 5-HT3 receptor antagonist antiemetics. The symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea,

vomiting, diarrhea). If concomitant use of CONCERTA® with a serotonergic drug is warranted, prompt recognition of the symptoms of serotonin syndrome is important so that treatment with methylphenidate and serotonergic drugs can be immediately discontinued and appropriate treatment instituted (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Sexual Function/Reproduction

Priapism

Prolonged and painful erections requiring immediate medical attention (sometimes including surgical intervention), have been reported with methylphenidate products, including CONCERTA® in both pediatric and adult patients (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**). Priapism can develop after some time on methylphenidate, often subsequent to an increase in dose. Priapism has also appeared during a period of methylphenidate withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained erections or frequent and painful erections should seek immediate medical attention.

Vascular

Peripheral Vasculopathy, Including Raynaud's Phenomenon

Stimulants used to treat ADHD, such as CONCERTA®, are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

Special Populations

Pregnant Women: 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.

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 alpha-phenyl-2-piperidine acetic acid (PPAA) in pregnant rats was 2 times that seen in trials in volunteers and patients with the maximum recommended dose of CONCERTA® based on the AUC.

There are no adequate and well-controlled studies in pregnant women. CONCERTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: 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 (see **ACTION AND CLINICAL PHARMACOLOGY**). Caution should be exercised if CONCERTA® is administered to a breast-feeding woman.

There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate. A risk to the suckling child cannot be excluded. A decision should be made whether to abstain from breast-feeding or to abstain from CONCERTA® therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the mother.

Pediatrics (< 6 years of age):
CONCERTA® should not be used in children under six years, since safety and efficacy in this age group have not been established. Long-term effects of methylphenidate in children have not been well established (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**).

Monitoring and Laboratory Tests
Periodic laboratory tests are advised during prolonged therapy. The tests should include, but not be limited to, haematological parameters, including complete blood count, differential and platelet counts, and liver enzymes.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The development program for CONCERTA® included exposures of 321 pediatric patients, and 305 adult patients to the drug in placebo-controlled, double-blind trials, and 3590 pediatric and adult patients in open-label clinical trials. The patients in these studies received CONCERTA® 18, 36, 54 or 72 mg/day. Children, adolescents, and adults with ADHD were evaluated in five placebo-controlled clinical studies (Studies 1, 2, and 3 in children; Study 4 in adolescents; Study 5 in adults), three open-label clinical trials and two open-label extensions. A limited number of adolescents and adults received CONCERTA® 72 mg/day (n=85) and 90 mg/day (n=41), respectively. Safety was assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events, except for Study 5 in adults, where MedDRA terminology was used.

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

Adverse Events Leading to Discontinuation of Treatment

Placebo-controlled Trials

In a 4-week, placebo-controlled, parallel-group trial (Study 3), one patient treated with CONCERTA® (0.9%; 1/106), one methylphenidate t.i.d.-treated patient (0.9%; 1/107), and one placebo-treated patient (1.0%; 1/99) discontinued due to an adverse event (sadness, emotional lability, and increase in tics, respectively).

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

In the 5-week placebo-controlled phase of a trial in adults (Study 5), 0% (0/96) of the patients in the placebo group, 1.0% (1/101) of the patients in the CONCERTA® 18 mg dose group, 2.9% (3/102) of the patients in the CONCERTA® 36 mg dose group and 7.8% (8/102) of the patients in the CONCERTA® 72 mg dose group discontinued due to an adverse event.

Open-Label Trials

In two open-label, long-term safety trials (Studies 6 and 7), one study up to 27 months in children aged 6 to 13 and one study up to 9 months in child, adolescent and adult patients treated with CONCERTA®, 6.7% (101/1514) of patients discontinued due to adverse events. Those events leading to discontinuation of CONCERTA®, with an incidence of >0.5%, included: insomnia (1.5%), twitching (tics, 1.0%), nervousness (0.7%), emotional lability (0.7%), abdominal pain (0.7%), and anorexia (0.7%).

Adverse Events Occurring in Patients Treated with CONCERTA®

Table 1.1 enumerates, for the 4-week placebo-controlled, parallel-group trial in children with ADHD at CONCERTA® doses of 18, 36, or 54 mg q.d., the incidence of treatment-emergent adverse events. The table includes only those events that occurred in 1% or more of patients treated with CONCERTA®, methylphenidate hydrochloride and placebo-treated patients.

Table 1.1: Incidence (%) of Treatment-Emergent Events[1] in a 4-Week Placebo-Controlled Clinical Trial of CONCERTA® in Children

Body Systems	Preferred Term[2]	CONCERTA® q.d. (n=106)	Methylphenidate hydrochloride t.i.d. (n=107)	Placebo (n=99)
General	Headache	14	6	10
	Abdominal pain	7	6	1
	Aggravation reaction	2	2	2
Digestive	Vomiting	4	2	3
	Anorexia	4	0	0
Nervous	Insomnia	4	1	1
	Dizziness	2	0	0
Respiratory	Upper respiratory tract infection	8	7	5
	Cough increased	4	8	2
	Pharyngitis	4	4	3
	Sinusitis	3	1	0

[1] Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 1%. Incidence greater than 1% has been rounded to the nearest whole number.
[2] COSTART terms

Table 1.2 lists the incidence of treatment-emergent adverse events for a 2-week placebo-controlled trial (Study 4) in adolescents with ADHD at CONCERTA® doses of 18, 36, 54 or 72 mg/day.

Table 1.2: Incidence (%) of Treatment-Emergent Events[1] in a 2-Week Placebo-Controlled Clinical Trial of CONCERTA® in Adolescents

Body Systems	Preferred Term[2]	CONCERTA®, q.d. (n=87)	Placebo (n=90)
General	Abdominal pain	2	2
	Accidental injury	6	3
	Allergic reaction	1	0
	Asthenia	2	2
	Chest pain	1	0
	Fever	3	0
	Flu syndrome	1	0
	Headache	9	8
	Infection	1	6
	Pain	1	1
Digestive	Anorexia	2	0
	Diarrhea	2	0
	Dyspepsia	1	0
	Gastrointestinal Disorder	1	0
	Increased appetite	1	0
	Nausea	1	2
	Tooth caries	1	0
	Vomiting	3	0
Musculoskeletal	Myalgia	1	0
Nervous	Agitation	1	0
	Anxiety	1	0
	Dizziness	1	0
	Insomnia	4	0
	Neurosis	1	1
	Tremor	1	0
Respiratory	Pharyngitis	2	1
	Rhinitis	3	2
Urogenital	Dysmenorrhea	2	0

[1] Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 1%. Incidence has been rounded to the nearest whole number.
[2] COSTART terms

Table 1.3 lists the incidence of treatment-emergent adverse events for a 5-week placebo-controlled trial (Study 5) in adults with ADHD at CONCERTA® doses of 18, 36, or 72 mg/day.

Table 1.3: Incidence (%) of Treatment-Emergent Events[1] in a 5-Week Placebo-Controlled Clinical Trial of CONCERTA® in Adults

Body System	Preferred Term[2]	CONCERTA®			Placebo
		18 mg q.d. (n=101)	36 mg q.d. (n=102)	72 mg q.d. (n=102)	q.d. (n=96)
Cardiac Disorders	Palpitations	2	5	5	0
	Tachycardia	4	5	8	0
Ear and Labyrinth Disorders	Vertigo	2	3	2	0
Gastrointestinal Disorders	Abdominal pain upper	4	2	2	5
	Diarrhea	3	1	4	5
	Dry mouth	8	7	21	2
	Hemorrhoids	0	0	4	0
	Nausea	8	16	15	4
General Disorders and Administration Site Conditions	Fatigue	4	4	6	6
Infectious and Infestations	Influenza	4	2	2	3
	Nasopharyngitis	7	8	4	9
Investigations	Weight decreased	3	8	11	5
Metabolism and Nutrition Disorders	Decreased appetite	20	22	34	7
Nervous System Disorders	Confusional state	0	3	1	0
	Dizziness	6	10	9	7
	Headache	26	21	17	18
	Initial insomnia	3	2	5	2
	Insomnia	12	12	17	7
	Migraine	0	1	3	3
	Paresthesia	3	1	1	0
	Tremor	1	1	7	1
Psychiatric Disorders	Aggression	2	3	2	1
	Agitation	0	1	3	1
	Anxiety	3	5	8	1
	Attention deficit/ Hyperactivity disorder	0	0	4	0
	Depressed mood	6	3	5	1
	Depression	0	3	4	1
	Irritability	4	4	9	1
	Nervousness	0	3	8	1
	Restlessness	0	2	6	0
	Tension	0	3	0	0
Respiratory, Thoracic and Mediastinal Disorders	Pharyngolaryngeal pain	2	0	4	1
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	5	3	8	1
Vascular Disorders	Hypertension	0	1	4	4

[1] Events, regardless of causality, for which the incidence in any CONCERTA® dosage group was at least 2%. Incidence has been rounded to the nearest whole number.
[2] MedDRA Terms

Adverse Events Occurring in Long-Term Safety Trials

CONCERTA® was evaluated in two long-term open-label studies (n=1514), one study up to 27 months in children aged 6 to 13 and one study up to 9 months in child, adolescent and adult patients. The adverse event profile seen is similar to that observed in shorter term trials. COSTART terminology is used to classify reported adverse experiences. The experiences are classified within body system categories and grouped by frequency.

Table 1.4: Adverse Events Occurring in Long-Term Safety Trials

Frequency	Very Frequent	Frequent		Less Frequent
Body System	**>10% - <50%**	**5-10%**	**<5% and ≥1%**	**<1%**
Body as a Whole	headache	accidental injury, abdominal pain, fever	flu syndrome, allergic reaction, infection, aggravation reaction, pain, extremity pain, back pain	surgery procedure, accidental overdose, chest pain, cyst, infection fungal, photosensitivity reaction, malaise, asthenia, neck pain
Cardiovascular System			hypertension	cardiovascular disorder, tachycardia, migraine
Digestive System		anorexia, vomiting	gastroenteritis, diarrhea, nausea, dyspepsia	rectal disorder, gastritis, increased appetite, nausea and vomiting, periodontal abscess, tongue disorder, tooth disorder, constipation
Endocrine System				diabetes mellitus
Hemic and Lymphatic System				ecchymosis, petechia, lymphadenopathy
Metabolic and Nutritional System			weight loss	Dehydration
Musculoskeletal System			myalgia	arthralgia, leg cramps
Nervous System	insomnia		twitching, nervousness, emotional lability, anxiety, depression, somnolence, hostility, dizziness	apathy, neurosis, hallucinations, speech disorder, sleep disorder, tremor, thinking abnormal, abnormal dreams
Respiratory System	upper respiratory tract infection	pharyngitis, cough increased, rhinitis	sinusitis, respiratory disorder, asthma bronchitis, epistaxis	dyspnea, pneumonia, voice alterations, laryngitis
Skin System			rash, contact dermatitis	pustular rash, urticaria, eczema, pruritus, skin benign neoplasm, acne, alopecia, nail disorder, psoriasis, herpes simplex
Special Senses		otitis media	conjunctivitis	ear disorder, diplopia, ear pain
Urogenital System				albuminuria, urinary frequency, urinary tract infection, urinary urgency

Tics

During two long-term, open-label studies, the overall incidence of tics (twitching) in children was 4.3% (48/1109 subjects). In one study, the incidence of tics rose from 3% at baseline to 5%

after one month. The incidence remained the same during the rest of the study. The treatment period was up to 27 months with a mean treatment duration of 10.3 months.

In a long-term study of up to 9 months of treatment, the incidence of tics was 0.4% (1/269) in adolescents and 0.7% (1/136) in adults.

Open-Label Adult Trials

In addition to the adverse events listed above, the following ADRs were reported in adult patients treated with CONCERTA® in open-label clinical trials of up to one year.

Table 1.5: Adverse Drug Reactions reported by CONCERTA®-Treated Subjects in 5 Open-Label Clinical Trials of Adult Subjects

Frequency	Very Frequent		Frequent	Less Frequent
Body System	**>10% - <50%**	**5-10%**	**<5% and ≥1%**	**<1%**
Blood and Lymphatic System Disorders				leukopenia
Cardiac Disorders			palpitations	
Eye Disorders			vision blurred	accommodation disorder, dry eye
Gastrointestinal Disorders	dry mouth		abdominal pain upper, abdominal discomfort	
General Disorders and Administration Site Conditions		irritability, fatigue	feeling jittery, pyrexia	thirst
Infections and Infestations		nasopharyngitis		
Investigations		blood pressure increased, heart rate increased		alanine aminotransferase increased
Metabolism and Nutrition disorders	decreased appetite			
Musculoskeletal and Connective Tissue Disorders			muscle spasms, muscle tightness	
Nervous System Disorder			psychomotor hyperactivity, paraesthesia	tension headache, sedation, lethargy,
Psychiatric Disorders		restlessness	Agitation, depressed mood, initial insomnia, libido decreased	affect lability, aggression, anger, bruxism, hypervigilance, mood altered, mood swings, panic attack, tearfulness, tension, confusional state
Reproductive system and Breast Disorders			erectile dysfunction	
Respiratory, Thoracic and Mediastinal Disorders			oropharyngeal pain	
Skin and Subcutaneous Tissue Disorder			hyperhidrosis	
Vascular Disorders				hot flush

All Clinical Trials (including open-labels trials, adult and pediatric)
Logorrhea was observed as an uncommon adverse reaction.

Post-Market Adverse Drug Reactions

Adverse events identified during post-marketing experience with CONCERTA® are included in Table 1.6.

In each table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000, including isolated reports

Table 1.6 Adverse Events Identified During Post-marketing Experience with CONCERTA®

Blood and Lymphatic System Disorders	
Very rare	Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura, Aplastic anemia
Cardiac Disorders	
Very rare	Arrhythmia
Immune System Disorders	
Rare	Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions and Exanthemas NEC, Serum sickness
Psychiatric Disorders	
Very rare	Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Mania, Complete Suicide, Suicide ideation, Suicide attempt, Psychotic disorder, Logorrhea, Libido disorder
Nervous System Disorders	
Very rare	Convulsion, Grand mal convulsion, Dyskinesia
Very rare	Cerebrovascular disorder (including Cerebral vasculitis, Cerebral hemorrhage, Cerebral arteritis, Cerebral vascular occlusion)
Eye Disorders	
Very rare	Diplopia, Mydriasis, Visual impairment
Cardiac Disorders	
Very rare	Angina pectoris, Bradycardia, Extrasystoles, Supraventricular tachycardia, Ventricular extrasystoles
Vascular Disorders	
Very rare	Raynaud's phenomenon
Hepatobiliary Disorders	
Very rare	Blood alkaline phosphatase increased, Blood bilirubin increased, Hepatic enzyme increased, Hepatocellular injury, Acute hepatic failure
Skin and Subcutaneous Tissue Disorders	
Very rare	Alopecia, Erythema, Dermatitis exfoliative, Stevens-Johnson Syndrome
Musculoskeletal and Connective Tissue Disorders	
Very rare	Arthralgia, Myalgia, Muscle twitching
Reproductive System and Breast Disorders	
Very Rare	Priapism
General Disorders and Administration Site Conditions	
Rare	Therapeutic response decreased
Very rare	Chest pain, Chest discomfort, Drug effect decreased, Hyperpyrexia, Sudden cardiac death
Investigations	
Very rare	Platelet count decreased, White blood cell count abnormal
Gastrointestinal Disorders	
Very rare	Pancreatitis
Endocrine Disorders	
Very rare	Hypoglycemia

Adverse Events with Other Methylphenidate Hydrochloride Products

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; abdominal pain; and weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, e.g., hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; and a few instances of scalp hair loss. There have been reports of serotonin syndrome following coadministration of methylphenidate with serotonergic drugs. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

Suicidal Behaviour and Ideation

There have been post-marketing reports of suicide-related events, including completed suicide, suicide attempt, and suicidal ideation in patients treated with ADHD drugs. In some of these reports, comorbid conditions may have contributed to the event. (see **WARNINGS AND PRECAUTIONS,** Suicidal Behaviour and Ideation)

DRUG INTERACTIONS

Overview

Alcohol may exacerbate the CNS adverse effect of psychoactive drugs. Therefore, patients undergoing CONCERTA® therapy should be advised to avoid alcohol during treatment.

Because of possible increases in blood pressure and heart rate, CONCERTA® should be used cautiously with drugs with similar pharmacological actions.

Drug-Drug Interactions

Because of possible increases in blood pressure, CONCERTA® should be used cautiously with vasopressor agents (see **WARNINGS AND PRECAUTIONS, Cardiovascular,** Hypertension and Other Cardiovascular Conditions).

Inhibition of Drug Metabolism by Methylphenidate

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

Antipsychotics
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.

Serotonergic Drugs
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.

Monoamine Oxidase Inhibitors
Methylphenidate is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result). The same precautions apply to CONCERTA® (see **CONTRAINDICATIONS**).

Clonidine
Serious adverse events, including sudden death, have been reported in concomitant use with clonidine. In these cases, no causality for the combination could be established because of insufficient data.

Drug-Food Interactions
There are no known food interactions with CONCERTA®.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
CONCERTA® should be administered starting at the lowest possible dose. Dosage should then be individually and slowly adjusted, to the lowest effective dosage, since individual patient response to CONCERTA® varies widely.

CONCERTA® should not be used in patients with symptomatic cardiovascular disease and should generally not be used in patients with known structural cardiac abnormalities (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Children: Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for sudden/cardiac death arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: a) are involved in strenuous exercise or activities, b) use other sympathomimetic ADHD drugs or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment with sympathomimetic medications, a personal and family history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during ADHD treatment should undergo a prompt cardiac evaluation. Patients who are considered to need extended treatment with CONCERTA® should undergo periodic evaluation of their cardiovascular status (see **WARNINGS AND PRECAUTIONS**).

Recommended Dose and Dosage Adjustment

General

CONCERTA® should be administered orally once daily in the morning, with or without food. For patients new to methylphenidate, the starting dose for CONCERTA® should be 18 mg daily. For patients currently on a methylphenidate-based product, see the conversion table below.

Dose Selection

Patients New to Methylphenidate

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

Table 1.7: Recommended Starting Dose and Maximum Dosage of CONCERTA® for Patients New to Methylphenidate

Patient Age	Recommended Starting Dose	Maximum Dosage
Children (6-12 years of age)	18 mg/day	54 mg/day
Adolescents (13-18 years of age)	18 mg/day	54 mg/day
Adults (>18 years of age)	18 mg/day	72 mg/day

A limited number of adolescents have been treated with CONCERTA® 72 mg/day in the open-label extension of Study 4 (n=62). A limited number of adults have been treated with doses above the recommended maximum daily dose, up to 90 mg/day (n=41 in study 5).

Patients Currently Using Methylphenidate Hydrochloride
The recommended conversion dose of CONCERTA® for patients who are currently taking methylphenidate hydrochloride b.i.d., t.i.d., or sustained-release (SR) at doses of 10 to 60 mg/day is provided in Table 1.8. Dosing recommendations are based on current dose regimen and clinical judgment.

Table 1.8: Recommended Dose Conversion from Methylphenidate Hydrochloride Regimens to CONCERTA®

Previous Methylphenidate Hydrochloride Daily Dose	Recommended CONCERTA® Conversion Dose
5 mg methylphenidate hydrochloride b.i.d./t.i.d. or 20 mg methylphenidate hydrochloride SR	18 mg q. a.m.
10 mg methylphenidate hydrochloride b.i.d./t.i.d.or 40 mg methylphenidate hydrochloride SR	36 mg q. a.m.
15 mg methylphenidate hydrochloride b.i.d./t.i.d. or 60 mg methylphenidate hydrochloride SR	54 mg q. a.m.
20 mg methylphenidate hydrochloride b.i.d./t.i.d	72 mg q. a.m.

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

Dose Titration
Dosage should be individualized according to the needs and responses of the patient. Based on an assessment of clinical benefit and tolerability, doses may be adjusted at weekly intervals for patients who have not achieved an optimal response.

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

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

Administration
CONCERTA® tablets must be swallowed whole with liquids, and must not be chewed, divided or crushed. In dogs, the intravenous injection of the pulverized CONCERTA® tablets resulted in death (see ***Product Monograph Part II*: TOXICOLOGY, Acute Toxicity**). 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 something that looks like a tablet in their stool.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Signs and Symptoms

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 convulsions, confusional state, hallucination (auditory and/or visual), hyperhidrosis, headache, pyrexia, tachycardia, palpitations, heart rate increased, sinus arrhythmia, hypertension, mydriasis and dry mouth.

Recommended Treatment

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate the 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® tablets should be considered when treating patients with overdose. Alcohol may induce the production of ethylphenidate. The amount of ethylphenidate production is proportional to the blood alcohol concentration (see **DRUG INTERACTIONS, Overview**). As with the management of all overdosage, the possibility of multiple drug ingestion, including alcohol, should be considered.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Methylphenidate hydrochloride is a central nervous system (CNS) stimulant. The mechanism of action on the CNS is not completely understood, but methylphenidate is thought to block the reuptake of dopamine and norepinephrine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Pharmacodynamics

Methylphenidate is a racemic mixture comprised of the *d*- and *l*-isomers. The *d*-isomer is pharmacologically active; the *l*-isomer has little pharmacologic activity. Following administration of CONCERTA® methylphenidate hydrochloride, plasma concentrations of the *l*-isomer were approximately 1/40th the plasma concentrations of the *d*-isomer.

Pharmacokinetics

Absorption: Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations reach an initial maximum at about 1 hour followed by gradual ascending concentrations over the next 5 to 9 hours. Mean times to reach peak plasma concentrations across all doses of CONCERTA® occurred between 6 to 10 hours. CONCERTA® once daily (q.d.) minimizes the fluctuations between peak and trough concentrations associated with multiple doses of immediate-release methylphenidate treatments (see Figure 1.1). The relative bioavailability of CONCERTA® q.d. and methylphenidate three times a day (t.i.d.) in adults is comparable.

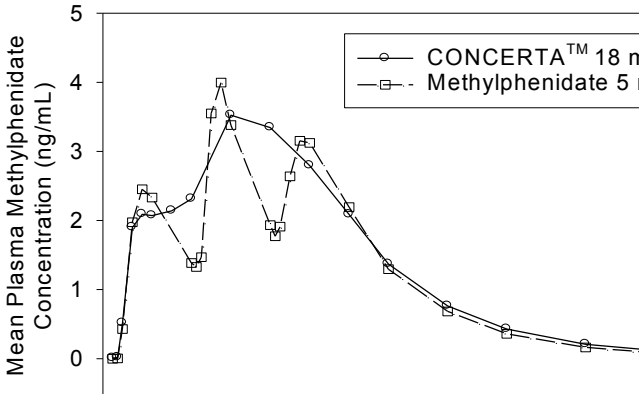


Figure 1.1: Mean methylphenidate plasma concentrations in 36 fasted adults, following a single dose of CONCERTA® 18 mg q.d. and immediate-release methylphenidate hydrochloride 5 mg t.i.d. administered every 4 hours.

Children (Single Dose)

The mean pharmacokinetic parameters in 13 children 7 to 12 years of age following administration of CONCERTA® 18, 36 or 54 mg are summarized in Table 1.9.

Table 1.9: Pharmacokinetic Parameters in Children after Single Dosing (Mean ± SD)

Parameters	CONCERTA® 18 mg (n=3)	CONCERTA® 36 mg (n=7)	CONCERTA® 54 mg (n=3)
C_{max} (ng/mL)	6.0 ± 1.3	11.3 ± 2.6	15.0 ± 3.8
T_{max} (h)	9.4 ± 0.02	8.1 ± 1.1	9.1 ± 2.5
$AUC_{0-11.5}$ (ng·h/mL)[#]	50.4 ± 7.8	87.7 ± 18.2	121.5 ± 37.3

[#] limited blood sampling

Adolescents (Steady-State)

The pharmacokinetics of methylphenidate were evaluated in adolescents 13 to 16 years of age with ADHD following steady-state dosing with CONCERTA® 36 mg, 54 mg, or 72 mg. The mean pharmacokinetic parameters are summarized in Table 1.10.

Table 1.10: Pharmacokinetic Parameters in Adolescents at Steady-State (Mean ± SD)

Parameters	CONCERTA® 36 mg (n = 10)	CONCERTA® 54 mg (n = 8)	CONCERTA® 72 mg* (n = 6)
C_{max} (ng/mL)	9.9 ± 5.5	12.8 ± 3.4	17.8 ± 4.5
T_{max} (h)	7.0 ± 2.1	6.8 ± 1.7	7.0 ± 1.8
AUC_{inf} (ng·h/mL)	112 ± 55.9	141 ± 34.3	186 ± 33.9
$t_{½}$ (h)	4.3 ± 2.0	3.6 ± 0.5	3.5 ± 0.5

* Not recommended. In the clinical study, only 62 adolescents received CONCERTA® at this dose level.

Adults

The mean single dose pharmacokinetic parameters in 36 healthy adults following the administration of CONCERTA® 18 mg q.d. and methylphenidate hydrochloride 5 mg t.i.d. are summarized in Table 1.11.

Table 1.11: Pharmacokinetic Parameters in Adult Subjects after Single Dosing (Mean ± SD)

Parameters	CONCERTA® (18 mg q.d.) (n=36)	Methylphenidate Hydrochloride (5 mg t.i.d.) (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 mean single dose and steady-state pharmacokinetic parameters in 25 healthy adults following the administration of CONCERTA® 54 and 72 mg q.d. are summarized in Table 1.12.

Table 1.12: Pharmacokinetic Parameters in Adult Subjects Following Single Dose and at Steady-State (Mean ± SD)

Parameters	CONCERTA® 54 mg (n=25)	CONCERTA® 72 mg (n=25)
Single Dose		
C_{max} (ng/mL)	12.03 ± 3.54	17.12 ± 5.80
T_{max}[a] (h)	6 (1-10)	6 (5-10)
AUC_{inf} (ng-h/mL)	130 ± 32.4	196 ± 65.7
$T_{½}$ (h)	3.58 ± 0.629	3.57 ± 0.617
Steady State		
C_{max} (ng/mL)	12.45 ± 2.84	16.12 ± 4.60
T_{max}[a] (h)	6 (1-10)	6 (5-8)
AUC_{tau} (ng-h/mL)	139 ± 33.6[b]	185 ± 49.0
$T_{½}$ (h)	3.60 ± 0.844	3.63 ± 0.49

[a] median and range are listed

[b] n=24

Distribution: Plasma methylphenidate concentrations in adults decline bi-exponentially following oral administration. The half-life of methylphenidate in adults following oral administration of CONCERTA® was approximately 3.5 h. In humans, 15 ± 5% of methylphenidate in the blood is bound to plasma proteins.

Metabolism and Excretion: In humans, methylphenidate is metabolized primarily by de-esterification to PPAA, which has little pharmacologic activity. In adults the metabolism of CONCERTA® q.d., as evaluated by metabolism to PPAA, is similar to that of methylphenidate t.i.d. The metabolism of single and repeated q.d. doses of CONCERTA® is similar. After oral dosing of radio-labelled 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 (see **ACTION AND CLINICAL PHARMACOLOGY; Special Populations and Conditions, Renal Insufficiency**).

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 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 during a dosing interval of the *d*-isomer and total methylphenidate increased proportionally with respect to dose.

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

Special Populations and Conditions

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® tablets, 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® have not been studied in children less than 6 years of age, and CONCERTA® should not be used in this patient population. There are no data available for the use of CONCERTA® in patients over 65 years of age.

Hepatic Insufficiency: CONCERTA® has not been studied in patients with hepatic insufficiency.

Renal Insufficiency: There is very limited experience with the use of methylphenidate in patients with renal insufficiency. Renal clearance is not significant for methylphenidate elimination, but the main methylphenidate metabolic product, PPAA, is predominantly (80%) cleared through the urine.

Nursing Women: A study conducted in rats indicated that the distribution profiles of methylphenidate in milk and plasma are similar. 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.

STORAGE AND STABILITY

Store at controlled room temperature (15-30ºC). Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

CONCERTA® extended-release tablets contain methylphenidate hydrochloride as the medicinal ingredient and are available in 18 mg, 27 mg, 36 mg and 54 mg dosage strengths. The 18 mg capsule-shaped tablets are yellow and printed with "alza 18". The 27 mg capsule-shaped tablets are gray and printed with "alza 27". The 36 mg capsule-shaped tablets are white and printed with "alza 36". The 54 mg capsule-shaped tablets are brownish-red and printed with "alza 54". All dosage strengths are supplied in bottles containing 100 tablets. In clinical studies, a dose of 72 mg was achieved by taking two 36 mg tablets. There is no 72 mg tablet available.

The dimensions of the CONCERTA® tablets are as follows in Table 1.13.

Table 1.13: Tablet Sizes

	18 mg Tablet	27 mg Tablet	36 mg Tablet	54 mg Tablet
Diameter	5.3 mm	5.3 mm	6.8 mm	6.8 mm
Length	12.0 mm	12.2 mm	15.0 mm	15.4 mm

Composition

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

System Components and Performance

CONCERTA® tablets use osmotic pressure to deliver methylphenidate hydrochloride at a controlled rate. The Osmotic Controlled-Release Oral Delivery (OROS®) 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, which consists of 22% of the drug dose, 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 6-7 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 digitally enhancing techniques are utilized.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

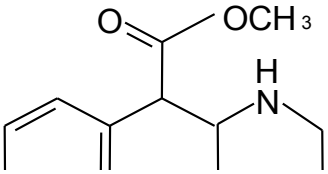
Drug Substance

Proper name: methylphenidate hydrochloride USP

Chemical name: *d,l* (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride

Molecular formula and molecular mass: $C_{14}H_{19}NO_2 \cdot HCl$, 269.77

Structural formula:



Physicochemical properties: methylphenidate hydrochloride USP is a white to off-white powder

pH: methylphenidate hydrochloride solutions are acidic to litmus

pKa: 8.9

Solubility: freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone

Melting Point: 224˚C to 226˚C

CLINICAL TRIALS

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

Study Demographics and Designs

Table 2.1: Demographics and Designs for Controlled Clinical Trials in Patients with ADHD					
Study	**Design**	**CONCERTA® Dose/Treatment Duration**	**# of Patients**	**Mean Age (years) [Range]**	**Primary Efficacy Variable**
Controlled Studies in Children					
Study 1	Double-blind, randomized, 3-period, 6-sequence crossover, placebo-controlled, comparative vs. IR methylphenidate	18, 36 or 54 mg once daily	64	9.2 [6-12]	IOWA Conners Rating scale for inattention/ overactivity
Study 2	Double-blind, randomized, placebo-controlled, active-controlled, crossover, comparative vs. IR methylphenidate	18, 36 or 54 mg once daily	70	9.1 [6-12]	IOWA Conners Rating scale for inattention/ overactivity
Study 3	Double-blind, randomized, placebo-controlled, active-controlled, parallel group vs. IR methylphenidate	18, 36 or 54 mg once daily	282	8.7 [6-12]	IOWA Conners Rating scale for inattention/ overactivity
Controlled Studies in Adolescents					
Study 4	Double-blind, randomized, placebo-controlled	titration to 72 mg once daily	220	14.7 [13-18]	Investigator ADHD rating scale
Controlled Studies in Adults					
Study 5	Double-blind, randomized, placebo-controlled, parallel group, dose-response	fixed doses of 18, 36 and 72 mg once daily	401	34.0 [18-63]	Investigator-rated Connors Adult ADHD Rating Scale (CAARS) total score

Children

Three double-blind, active- and placebo-controlled studies were conducted in 416 children aged six to twelve. The controlled studies compared CONCERTA® q.d. (18, 36 or 54 mg), methylphenidate hydrochloride t.i.d. over 12 hours (15, 30 or 45 mg total daily dose), and placebo in two single-centre, 3-week, crossover studies (Study 1 and Study 2) and in a multicentre, 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 school teachers using the Inattention/Overactivity with Aggression (IOWA) Conners scale. Significant reduction in the Inattention/Overactivity subscale in the treatment group versus the placebo was shown consistently across all three controlled studies for CONCERTA® q.d. and methylphenidate hydrochloride t.i.d. ($p < 0.001$). The scores for the placebo-controlled parallel study for all three

treatment groups are presented in Figure 2.1.

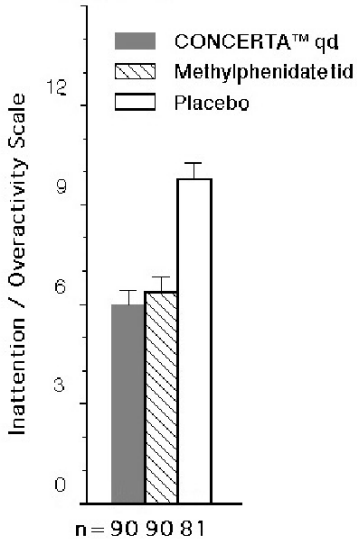


Figure 2.1: Mean community school teacher IOWA Conners Inattention/Overactivity scores with CONCERTA® q.d. (18, 36 or 54 mg), methylphenidate hydrochloride t.i.d. over 12 hours (15, 30 or 45 mg total daily dose), and placebo. The study involved 4 weeks of parallel-group treatments with a Last Observation Carried Forward analysis for weeks 2 to 4. Data at Week 4 is shown. Error bars represent mean plus standard error of the mean.

Studies 1 and 2

In the two placebo-controlled crossover studies (Studies 1 and 2), symptoms of ADHD were evaluated by laboratory school teachers using the SKAMP (Swanson, Kotkin, Agler, M-Flynn and Pelham) laboratory school rating scale. Significant improvement in attention and behaviour versus placebo was shown consistently across the two studies ($p < 0.005$). Efficacy was maintained through 12 hours after dosing, and the sustained beneficial effects of CONCERTA® q.d. therapy seen throughout the laboratory classroom day were comparable in duration to those with methylphenidate hydrochloride t.i.d. Figure 2.2 presents the laboratory school teacher SKAMP ratings for CONCERTA® q.d., methylphenidate hydrochloride t.i.d. and placebo in Study 1. Similar results were obtained in Study 2.

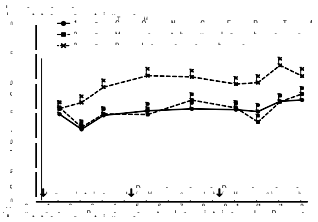


Figure 2.2: Mean laboratory school teacher SKAMP Ratings of Combined Attention (Study 1) with CONCERTA® q.d. (18, 36 or 54 mg), methylphenidate hydrochloride t.i.d. over 12 hours (15, 30 or 45 mg total daily dose) and placebo. Error bars represent mean plus standard error of the mean. The sample sizes for CONCERTA®, methylphenidate hydrochloride t.i.d., and placebo groups were 60, 62 and 60, respectively.

Adolescents (Study 4)

In a randomized, double-blind, multicentre, placebo-controlled trial (Study 4) involving 177 patients, CONCERTA® was demonstrated to be effective in the treatment of ADHD and was well tolerated in adolescents aged 13 to 18 at doses up to 72 mg/day (1.4 mg/kg/day). Of 220 patients who entered an open 4-week titration phase, 177 were titrated to an individualized dose (maximum 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 for CONCERTA® were significantly improved relative to placebo (CON –14.93; PLA –9.58; p=0.001). Mean scores for CONCERTA® and placebo, respectively, at the end of the double-blind phase were 16.62 and 21.40, compared to 31.55 and 30.99 at baseline.

Adults (Study 5)

This was a 5-week, randomized, double-blind, multicentre, placebo-controlled, dose-response trial (Study 5) was conducted in 401 adults with ADHD aged 18 to 65 years using once daily CONCERTA® fixed doses of 18 mg, 36 mg and 72 mg. Efficacy was evaluated by the mean change from baseline to double-blind endpoint in the investigator-rated Connors' Adult ADHD Rating Scale (CAARS) total score. All doses of CONCERTA® (18 mg, 36 mg and 72 mg/day) were statistically significantly superior to placebo in improving the CAARS total scores at double-blind endpoint compared to baseline (mean change of -7.6 for placebo, -10.6 (p=0.0146)

for CONCERTA® 18 mg, -11.5 (p=0.0131) for CONCERTA® 36 mg and -13.7 (p<0.0001) for the CONCERTA® 72 mg). Statistically significant differences compared to placebo were first observed at Week 1. Secondary endpoints included the investigator-rated Clinical Global Impressions - Severity (CGI-S) and the CAARS-S:S (patient-rated CAARS scale). The results from the secondary endpoints were consistent with the primary endpoint.

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

Methylphenidate hydrochloride is a sympathomimetic agent classified as a central nervous system (CNS) stimulant. Its mechanism of action is not entirely understood; however, it blocks the reuptake and enhances the release of dopamine and norepinephrine in the mammalian brain, an effect that increases dopamine and norepinephrine levels in the synaptic cleft. In vitro radioligand binding studies demonstrate that binding of methylphenidate in the brain is localized to dopamine-rich areas. Methylphenidate releases dopamine from a reserpine-sensitive storage pool and inhibits the catecholamine metabolic enzyme, monoamine oxidase (MAO), in the brain of rats.

Methylphenidate is a racemic mixture comprised of the *d*- and *l*-threo stereoisomers. The *d*-isomer is pharmacologically active; the *l*-isomer has little pharmacologic activity. In a number of animal models, methylphenidate enhances locomotor activity and induces stereotypic behaviours. Recent clinical findings in ADHD children suggest an abnormality in the dopamine transporter gene (DAT_1), the D_4 receptor gene (DRD-4) and/or the D_2 receptor gene that may be at least partly overcome by the dopaminergic effects of methylphenidate, suggesting a possible mode of action.

Safety Pharmacology

Methylphenidate hydrochloride had no effect in hERG-transfected cells or on the action potential of guinea pig papillary muscles. The no observed adverse effect level (NOAEL) for stimulatory effects on the cardiovascular system in conscious dogs (increased blood pressure and heart rate) was 10 mg/kg. The NOAEL for stimulatory effects on the respiratory system in free-moving rats was 3 mg/kg. The NOAEL for methylphenidate hydrochloride's convulsion evoking action in mice was 10 mg/kg.

Pharmacokinetics

Studies primarily in humans and rats, as well as limited information available for mice, dogs, monkeys and other species, demonstrate that methylphenidate is readily absorbed, distributed, metabolized and eliminated regardless of the route of administration. While the kinetic rates for these processes are similar among different species, there are differences in metabolic profiles. Distribution of metabolites differs from that of the unchanged parent material, with most of the material that reaches the brain consisting of the unchanged parent compound. Biotransformation in the gut or first-pass metabolism, or both, is common among the species studied. The primary metabolite in humans and a major metabolite in other species is alpha-phenyl-alpha-(2-piperidyl)

acetic acid (PPAA), also commonly called ritalinic acid. Pharmacokinetic data showed dose-dependent exposure to methylphenidate and PPAA in adult animals; in juvenile rats, exposure was more than dose-proportional. In the presence of alcohol, an intermediate metabolite, ethylphenidate, is produced. The amount of ethylphenidate production is proportional to the blood alcohol concentration. Excretion of radioactivity into breast milk was observed after single oral administration of 5 mg/kg ^{14}C-methylphenidate hydrochloride to lactating rats.

TOXICOLOGY

The toxicology program for methylphenidate and the oral controlled-release OROS methylphenidate dosage form consists of acute toxicity, long-term toxicity, carcinogenicity and mutagenicity, reproductive and developmental toxicity, and other special toxicity studies.

Acute Toxicity

The acute toxicity of methylphenidate hydrochloride has been studied primarily in mice and rats, and additionally in rabbits and dogs. Published oral LD_{50} values for rodents and rabbits range from approximately 190 to 900 mg/kg. The probable cause of death in LD_{50} studies was excessive central adrenergic stimulation. Clinical signs noted with high doses of methylphenidate in animal acute toxicity studies include agitation and increased motor activity, tremors and convulsions, decreased food consumption and stereotypic behaviours such as licking or gnawing.

A dog study was conducted to study the abuse potential of CONCERTA® (N=8) and immediate release methylphenidate (N=8). The dogs were intravenously administered with pulverized CONCERTA® or methylphenidate tablets mixed with liquid. Death occurred after a single 0.5 mg or 1 mg/kg dose of CONCERTA®. Mortality was not observed in methylphenidate-treated dogs dosed at 1 mg/kg/day for 2 weeks. It is likely that the deaths were due the particles present in the pulverized CONCERTA® tablets.

Long-Term Toxicity

Treatment with methylphenidate hydrochloride at repeated high doses has demonstrated transient effects on body weight in rats and mice. The liver was the primary target organ for toxicity in mice and rats, with male mice being the most sensitive showing hepatocellular degeneration. Methylphenidate has shown some effects on maturation and estrous cyclicity in neonatal rats; estrous cycles were reversibly affected in older rats. Reversible effects of methylphenidate were seen on skeletal growth in neonatal rats; such effects were not seen in older rats. Endocrine effects of MPH have generally been inconsistent or did not show a dose response. The potential gastrointestinal (GI) effects and systemic toxicity of the OROS methylphenidate dosage form were evaluated in a study conducted in dogs. Except for excessive salivation, no other treatment-related clinical signs were observed. No treatment-related findings were seen in body or organ weights, physical exams, ophthalmic exams, qualitative food consumption, hematology, clinical chemistry, urinalysis, macroscopic exams or histopathologic evaluation of tissues. No treatment-related GI irritation or systemic effects were seen for oral doses up to 72 mg/day for 30 days.

A second study in beagle dogs was conducted to determine the possible local gastrointestinal and systemic effects of CONCERTA® after daily administration (0, 72, 144 or 216 mg/day) for 4 weeks. Females in all CONCERTA® groups showed toxicologic effects such as hyperactivity, reduced food consumption, and decreased mean body weight gain; in males similar effects were seen only in the two higher CONCERTA® groups (144 and 216 mg/day). However, with the exception of mean body weight gain in 216 mg/day females, the CONCERTA®-related changes resolved during recovery.

Carcinogenicity and Mutagenicity

In a lifetime carcinogenicity study carried out in B6C3F1 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 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 tumour type. There was no increase in total malignant hepatic tumours. The mouse strain used is sensitive to the development of hepatic tumours, and the significance of these results to humans is unknown.

Methylphenidate hydrochloride did not cause any increases in tumours 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 hydrochloride.

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.

Reproductive and Developmental Toxicity

Studies have been conducted in mice, rats and rabbits to evaluate the potential reproductive and developmental toxicity of methylphenidate. Rats appear to be a better animal model than rabbits for developmental/reproductive studies of methylphenidate, based on plasma AUC ratios of drug:metabolite.

Reproductive toxicity was studied using a Reproductive Assessment by Continuous Breeding (RACB) protocol or Sperm Morphology Vaginal Cytology Evaluations (SMVCE) endpoints to assess male and female reproductive functions. Methylphenidate hydrochloride 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. A perinatal and postnatal development study with neurobehavioural assessments in rats indicated slight developmental delay and marginal alterations in neuromotor performance in offspring of the high-dose dams treated with 30 mg/kg/day methylphenidate hydrochloride (approximately 15 and 3 times the maximum recommended daily human dose for CONCERTA® tablets [54 mg methylphenidate hydrochloride] on a mg/kg and mg/m^2 basis, respectively). No effects on learning and memory were seen in offspring and no adverse effects were noted in offspring of dams treated with methylphenidate hydrochloride doses of 12.5 mg/kg/day and lower.

A teratology study conducted in rats supports the conclusion that methylphenidate is not a developmental toxicant at the dose levels tested, up to 30 mg/kg/day. The maternal no-observed-adverse-effect level (NOAEL) of methylphenidate hydrochloride was 5 mg/kg/day. No adverse effects on embryo/fetal viability, growth or malformations were seen. The developmental toxicity NOAEL of methylphenidate hydrochloride was at least 30 mg/kg/day. In a study conducted in rabbits, methylphenidate hydrochloride was shown to have teratogenic effects 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.

Weaning juvenile rats (F_0) of both sexes were administered methylphenidate hydrochloride at total daily doses of 5, 12.5, and 30 mg/kg for approximately 4.5 months. The no observed adverse effect level (NOAEL) for F_0 juvenile toxicity was considered to be 12.5 mg/kg/day for males and 30 mg/kg/day for females. For F_1 developmental toxicity the NOAEL was considered to be 12.5 mg/kg/day.

Other Special Toxicity Studies

Five system transit and drug release studies conducted with the OROS methylphenidate dosage form in dogs showed no unexpected clinical signs during transit through the gastrointestinal (GI) tract. Membrane shells remained intact during GI transit with cumulative release of active ingredient generally comparable in vitro and in vivo.

Cellular toxicity profile of methylphenidate and effects of methylphenidate on mitochondrial function were evaluated in vitro using an MTT(3-[4,5-dimethythiazole-2-yl]-2,5-di-phenyl-tetrazolium bromide) assay. Results demonstrated that MPH in cell culture medium, at approximate concentrations of 0.125 and 0.25 mg/mL, was noncytotoxic to L-929 mouse fibroblast cells.

REFERENCES

Preclinical

1. Aoyama T, Kotaki H, Iga T. Dose-dependent kinetics of methylphenidate enantiomers after oral administration of racemic methylphenidate to rats. J Pharmacobio-Dyn 1990; 13:647-652.
2. Bhattacharyya AK, Ghosh B, Aulakh CS, Pradhan SN. Correlation of behavioral and neurochemical effects of acute administration of methylphenidate in rats. Prog Neuro-Psychopharmacol 1980; 4:129-136.
3. Chapin RE, Sloane RA. Reproductive assessment by continuous breeding: Evolving study design and summaries of 90 studies. Environ Health Perspect 1997; 105(Suppl. 1):199-395.
4. Cook EH, Stein MA, Krasowski MD, Cox NJ, Olkon DM, Kieffer JE, Leventhal BL. Association of attention-deficit disorder and the dopamine transporter gene. Am J Hum Genetics 1995; 56:993-998.
5. Costall B, Naylor RJ. The involvement of dopaminergic systems with the stereotyped behavior patterns induced by methylphenidate. J Pharm Pharmacol 1974; 26:30-33.
6. Dunnick JK, Hailey JR. Experimental studies on the long-term effects of methylphenidate hydrochloride. Toxicol 1995; 103:77-84.
7. Egger H, Bartlett F, Dreyfuss R, Karliner J. Metabolism of methylphenidate in dog and rat. Drug Metab Dispos 1981; 9:415-423.
8. Faraj BA, Israili ZH, Perel JM, Jenkins ML, Holtzman SG, Cucinell SA, Dayton PG. Metabolism and disposition of methylphenidate-14C: Studies in man and animals. J Pharmacol Exp Ther 1974; 191:535-547.
9. Gerlach J, Bjørndal N, Christensson E. Methylphenidate, apomorphine, THIP, and diazepam in monkeys: Dopamine-GABA behavior related to psychoses and tardive dyskinesia. Psychopharmacology 1984; 82:131-134.
10. Hendley ED, Snyder SH, Fauley JJ, Lapidus JB. Stereoselectivity of catecholamine uptake by brain synaptosomes: Studies with ephedrine, methylphenidate, and phenyl-2-piperidyl carbinol. J Pharmacol Exper Ther 1972; 183:103-116.
11. Hoffman BB, Lefkowitz RJ. Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In Hardman JG, Limbird LL, Molinoff PB, Ruddon RW, Goodman AG, eds, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed. New York: McGraw-Hill 1996; 199-248.
12. Meier R, Gross F, Tripod J. Ritalin, eine neuartige synthetische verbindung mit spezifischer zentralerregender wirkungskomponente. Klin Wochenscr 1954; 32:445-450.
13. Morrissey RE, Schwetz BA, Lamb JC, Ross MD, Teague JL, Morris RW. Evaluation of rodent sperm, vaginal cytology, and reproductive organ weight data from National Toxicology Program 13-week studies. Fundam Appl Toxicol 1988; 11:343-358.

14. National Toxicology Program (NTP). Toxicology and Carcinogenesis Studies of Methylphenidate Hydrochloride (CAS No. 298-59-9) in F344/N Rats and B6C3F1 Mice (Feed Studies). NTP TR No. 439, NIH Publication No. 95-3355. US Dept of Health & Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC, 1995.

15. National Toxicology Program (NTP). Methylphenidate•HCl: Reproduction and Fertility Assessment in Swiss CD-1 Mice When Administered via Feed. Study No. NTP-87-FACB-055. US Dept of Health & Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC, 1989.

16. Shih TM, Khachaturian ZS, Hanin I. Involvement of both cholinergic and catecholaminergic pathways in the central action of methylphenidate: A study utilizing lead-exposed rats. Psychopharmacology 1977; 55:187-193.

17. Sipes IG, Carter DE. The disposition and metabolism of methylphenidate hydrochloride (MPH HCl) in rats and mice. National Institute of Environmental Health Sciences Contract No. NO1-ES-3-5031. Final Draft Report, 13 August 1990.

18. Szporny L, Görög P. Investigations into the correlations between monoamine oxidase inhibition and other effects due to methylphenidate and its stereoisomers. Biochem Pharmacol 1961; 8:263-268.

19. Thai DL, Sapko MT, Reiter CT, Bierer DE, Perel JM. Asymmetric synthesis and pharmacology of methylphenidate and its para-substituted derivatives. J Med Chem 1998; 41(4):591-601.

20. Usdin E, Efron DH. Psychotropic Drugs and Related Compounds, 2nd ed. Rockville, MD: National Institute of Mental Health, Department of Health, Education, and Welfare 1972; DHEW Publication No. (HSM) 72-9074; 263-264.

21. Warawa EJ, Mueller NJ. Quinuclidine Chemistry. 3.-cis-2-(4'-chlorobenzhydryl)-3-quinuclidinol, a new central nervous system stimulant. Importance of the benzhydryl configuration. J Med Chem 1975; 18:71-74

22. Wargin W, Patrick K, Kilts C, Gualtieri CT, Ellington K, Mueller RA, Kraemer G, Breese GR. Pharmacokinetics of methylphenidate in man, rat and monkey. J Pharmacol Exp Ther 1983; 226:382-386.

23. Woods SK, Meyer JS. Exogenous tyrosine potentiates the methylphenidate-induced increase in extracellular dopamine in the nucleus accumbens: A microdialysis study. Brain Res 1991; 560:97-105.

Clinical

24. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed.). Washington, DC: 1994; 78-85.

25. Biederman J, Mick E, Surman C, Doyle R, Hammerness P, Harpold T, Dunkel S, Dougherty M, Aleardi M, Spencer T. A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2006; 59:829-835.

26. Biederman J, Mick E, Surman C, Doyle R, Hammerness P, Harpold T, Dunkel S, Dougherty M, Aleardi M, Spencer T. An open-label trial of OROS methylphenidate in adults with late-onset ADHD. CNS Spectr. 2006; 11(5): 390-396.

27. CPS Position Statement. The use of stimulant medication in the treatment of attention deficit hyperactivity disorder. Paediatr Child Health 2002; Vol. 7 No. 10: 693-696.

28. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD Rating Scale – IV: Checklists, Norms and Clinical Interpretation. New York: Guilford Press; 1998.

29. Fallu A, Richard C, Prinzo R, Binder C. Does OROS*-methylphenidate improve core symptoms and deficits in executive function? Results of an open-label trial in adults with attention deficit hyperactivity disorder. Curr Med Res Opin 2006; 22(12): 2557-2566.

30. Hardman J, Goodman Gilman A, Limbird LE. Goodman and Gilman's The Pharmacological Basis of Therapeutics 9th ed. McGraw-Hill Inc 1996; 219-221.

31. Loney J, Milich R. Hyperactivity, inattention, and aggression in clinical practice. In: Wolraich M and Routh DK eds, Advances in Developmental and Behavioral Pediatrics, 3rd ed. Greenwich, CT: JAI Press 1982; 113-147.

32. Medori R, Ramos-Quiroga A, Casas M, Kooij JJS, Niemelä A, Trott G-E, Lee E, Buitelaar JK. A randomized, placebo-controlled trial of three fixed dosages of prolonged-release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2008; 63:981-989.

33. Modi NB, Wang B, Noveck RJ, Gupta SK. Dose-proportional and stereospecific pharmacokinetics of methylphenidate delivered using an osmotic, controlled-release oral delivery system. J Clin Pharmacol 2000; Vol. 40 No. 10:1141-1149.

34. Modi NB, Wang B, Hu WT, Gupta SK. Effect of food on the pharmacokinetics of osmotic controlled-release methylphenidate HCl in healthy subjects. Biopharm Drug Dispos 2000; 21:23-31.

35. Modi NB, Lindemulder B, Gupta SK. Single and multiple-dose pharmacokinetics of an oral once-a-day osmotic controlled-release OROS® (methylphenidate HCl) formulation. J Clin Pharmacol 2000; 40:379-388.

36. Markowitz JS Devane CL, Boulton DW, Nahas Z, Risch C, Diamond F, Patrick KS. Ethylphenidate formation in human subjects after the administration of a single dose of methylphenidate and ethanol. Drug Metab Dispo 2000;28(6):620-4.

37. Olson KR. Poisoning and Drug Overdose 4th ed. Mc Graw-Hill 2004; 72-74.

38. Palumbo D, Spencer T, Lynch J, Co-Chien G, Faraone SV. Emergence of tics in children with ADHD: Impact of once-daily OROS methylphenidate therapy. J Child Adolesc Psychopharmacol 2004;14(2):185-94.

39. Pelham WE, Gnagy EM, Burrows-Maclean L, Williams A, Fabiano GA, Morrisey SM, Chronis AM, Forehand GL, Nguyen CA, Hoffman MT, Lock TM, Fiebelkorn K, Coles EK, Panahon CJ, Steiner RL, Meichenbaum DL, Onyango AN, Morse GD. Once-a day CONCERTA® methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. PEDIA 2001; Vol. 107 No. 6:1-15.

40. Pelham WE, Jr., Milich R, Murphy DA, and Murphy HA. Normative data on the IOWA Conners teacher rating scale. J Clin Child Psychol 1989; 18:259-262.

41. Swanson J, Gupta S, Lam A, et al. Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2003; 60:204-211.

42. Swanson JM, Gupta S, Williams L, et al. Efficacy of a new pattern of delivery of methylphenidate for the treatment of ADHD: effects on activity level in the classroom and on the playground. J Am Acad Child Adolesc Psychiatry 2002; 41(11):1306-1314.

43. Swanson J, Gupta S, Guinta D, Flynn D, Agler D, Lerner M, Williams L, Shoulson I, Wigal S. Acute tolerance of methylphenidate in the treatment of attention deficit hyperactivity disorder in children. Clin Pharmacol Ther 1999; 66(3):295-305.

44. Swanson J, Greenhill L, Pelham W, Wilens T, Wolraich M, Abikoff H, Atkins M, August G, Biederman J, Bukstein O, Conners CK, Efron L, Fiebelkorn K, Fried J, Hoffman M, Lambrecht L, Lerner M, Leventhal B, McBurnett K, Morse E, Palumbo D, Pfiffner L, Stein M, Wigal S, Winans E. Initiating CONCERTA™ (OROS® methylphenidate HCl) qd in children with attention-deficit hyperactivity disorder. J Clin Research 2000; 3:59-76.

45. Swanson JM. The SKAMP Rating Scale. In: Swanson J ed, School-based Assessments and Interventions for ADD Students. Irvine, CA: KC Publishing 1992; 65-69.

46. Swanson JM, Kraemer HC, Hinshaw SP, et al. Clinical relevance of the primary findings of the MTA: Success rates based on severity of ADHD and ODD symptoms at the end of treatment. J Am Acad Child Adolesc Psychiatry 2001; 40(2):168-179.

47. The MTA Cooperative Group. A 14-month randomized Clinical Trial of Treatment Strategies for Attention-Deficit/Hyperactive Disorder. Arch Gen Psychiatry 1999; 56: 1073-1086.

48. Topol EJ. Textbook of Cardiovascular Medicine 2nd ed. Lipincott Williams and Williams 2002; 874.

49. Wilens T, Pelham W, Stein M, et al. ADHD treatment with once-daily OROS® methylphenidate: interim 12-month results from a long-term open-label study. J Am Acad Child Adolesc Psychiatry 2003; 42(4):424-433.

50. Wolraich ML, Greenhill LL, Pelham W, et al. Randomized, controlled trial of OROS® methylphenidate once a day in children with attention-deficit/hyperactivity disorder. Pediatrics 2001; 108(4):883-892.

PART III: CONSUMER INFORMATION

CONCERTA®
methylphenidate hydrochloride
Extended-release Tablets

This leaflet is part III of a three-part "Product Monograph" published when CONCERTA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CONCERTA®. Contact your doctor or pharmacist if you have any questions about the drug.

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

Please read this before you/your child start taking CONCERTA® tablets. Remember, this information does not take the place of your doctor's instructions.

ABOUT THIS MEDICATION

What the medication is used for:
CONCERTA® is a once-a-day treatment for Attention Deficit Hyperactivity Disorder, or ADHD, in children 6 years of age or older, adolescents and adults. CONCERTA® is a central nervous system stimulant. CONCERTA® contains a medicinal ingredient that has been used to treat ADHD for more than 30 years.

ADHD has three main types of symptoms: inattention, hyperactivity and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all three types of symptoms. Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis.

Symptoms of ADHD in adults may include a lack of organization, problems starting tasks, impulsive actions, daydreaming, slow processing of information, difficulty learning new things, irritability, lack of esteem and excessive effort to maintain some organization.

What it does:
CONCERTA® tablet uses Osmotic Controlled-Release Oral Delivery System (OROS®) to release the medication in a controlled way throughout the day. Part of the CONCERTA® tablet dissolves right after you / your child swallow it in the morning, giving you / your child an initial dose of medication. The rest of the medication is slowly released during the day to keep improving the symptoms of ADHD. CONCERTA® helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

When it should not be used:
You / your child should NOT take CONCERTA® if you / your child:
- are allergic to methylphenidate hydrochloride or any of the other ingredients in CONCERTA®;
- have glaucoma, an eye disease
- have symptomatic cardiovascular disease;
- have moderate to severe high blood pressure;
- have advanced arteriosclerosis (hardened arteries);
- have hyperthyroidism (an overactive thyroid gland); or
- are taking or have taken within the past 14 days monoamine oxidase inhibitors (a type of drug, see **INTERACTIONS WITH THIS MEDICATION**).

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

What the medicinal ingredient is:
methylphenidate hydrochloride

What the nonmedicinal ingredients are:
butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide and triacetin

What dosage forms it comes in:
extended-release tablets: 18 mg, 27 mg, 36 mg and 54 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Drug Dependence**
  Abuse of CONCERTA® can lead to dependence. Tell your doctor if you have ever abused or been dependent on alcohol or drugs, or if you are now abusing or dependent on alcohol or drugs

The following have been reported with use of CONCERTA® and other medicines used to treat ADHD.

1. **Heart-related problems:**
- **sudden death in patients who have heart problems or heart defects**
- **stroke and heart attack in adults**
- **increased blood pressure and heart rate**

Sudden death has been reported in association with stimulant drugs for ADHD treatment in children with structural heart abnormalities. CONCERTA® generally should not be used in children, adolescents or adults with known structural heart abnormalities.

Tell your doctor if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your doctor may wish to check you or your child carefully for heart problems before starting CONCERTA®.

Your doctor may wish to check you or your child's blood pressure and heart rate regularly during treatment with CONCERTA®.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking CONCERTA®.

2. <u>Mental (Psychiatric) problems:</u>

- **New or worse thoughts or feelings related to suicide (thinking about or feeling like killing oneself) and suicide actions (including suicide attempt, suicidal ideation and completed suicide)**
- **new or worse symptoms of bipolar illness, characterized by extreme mood swings, with periods of mania (unusually excited, over-active or un-inhibited) alternating with periods of depression (feelings of sadness, worthlessness or hopelessness)**
- **new or worse aggressive behaviour or hostility**
- **new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms**

These new or worse mental symptoms may be more likely to occur if you/your child have mental disorders that you may or may not know about. Tell your doctor about any mental problems or about any personal or family history of suicide, bipolar illness, or depression you or your child have.

A small number of patients taking ADHD drugs may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of suicide, self-harm or harm to others. Those suicidal thoughts or behaviors may occur at any time during treatment, particularly at the start or during dose changes, and also after stopping CONCERTA®. **Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your doctor immediately. Close observation by a doctor is necessary in this situation.**

Call your doctor right away if you or your child have any new or worsening mental symptoms or problems while taking CONCERTA®, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

BEFORE you or your child uses CONCERTA®, talk to your doctor or pharmacist if you / your child:

- have structural heart abnormalities;
- have tics (movements or sounds that you cannot control) or Tourette's syndrome, or if someone in your family has tics or Tourette's syndrome;
- have eye problems, such as:
  - increased pressure in the eye
  - far-sightedness (difficulty seeing near objects)
- have mental problems or family history of mental problems, including psychosis, mania, bipolar illness, depression or suicide;
- become aggressive, anxious or agitated, or feel more aggressive, anxious or agitated than usual;
- have mild high blood pressure;
- take blood pressure medications;
- take cold, allergy or other drugs that can affect blood pressure;
- have a narrowing or blockage of your gastrointestinal tract (your esophagus, stomach, or small or large intestine);
- have a family history of sudden death or death related to heart problems;
- do strenuous exercise;
- take other drugs for ADHD;
- have or have had any disorder of the blood vessels in the brain (e.g., aneurysm, stroke, vasculitis), or
- have circulation problems in fingers and toes, including numbness; feeling cold or pain. (This is also known as Raynaud's).

Tell your doctor ***immediately*** if you / your child develop any of the above conditions or symptoms while taking CONCERTA®. He/she will decide if you can start/continue taking CONCERTA®.

BEFORE taking CONCERTA®, tell your doctor if you are pregnant or plan to become pregnant.

Tell your doctor if you are nursing a baby. Methylphenidate passes into breast milk. If you take CONCERTA®, it can be in your breast milk. You should consult with your doctor to determine whether you should stop breast-feeding or discontinue CONCERTA®.

Your doctor will monitor your progress with CONCERTA® and may require you to do occasional tests to ensure your health and safety.

INTERACTIONS WITH THIS MEDICATION

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

- type of medicine for depression or anxiety called a 'selective serotonin reuptake inhibitor' (SSRI) or a 'serotonin and norepinephrine reuptake inhibitor' (SNRI);
- clonidine;
- type of medication called an "antipsychotic";
- other medicines that a doctor has prescribed;
- medicines that you buy yourself without a prescription

- any herbal remedies that you /your child may be taking.

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

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

You should avoid alcoholic drinks while taking CONCERTA®.

CONCERTA® may change the way your / your child's body reacts to certain medicines. These include medicines used to treat depression (e.g., amitriptyline, imipramine and fluoxetine), prevent seizures (e.g., phenobarbitone, phenytoin, carbamazepine and primidone) or prevent blood clots (commonly called "blood thinners", e.g., warfarin). Your doctor may need to change your / your child's dose of these medicines if you / your child are taking them with CONCERTA®.

PROPER USE OF THIS MEDICATION

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

Take CONCERTA® once each day in the morning with or without food.

CONCERTA® has not been studied and should not be used in children under six years of age. CONCERTA® has not been studied in adults over 65 years of age.

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

CONCERTA® may be a part of your / your child's overall treatment for ADHD. Your doctor may also recommend that you / your child have counselling or other therapy.

As with all medicines, never share CONCERTA® with anyone else.

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

Overdose:

In case of a drug overdose, immediately go to the nearest emergency room even if you do not feel sick. Make sure you take your medicine bottle with you to show the doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Refer to the beginning of this leaflet for information on reported heart-related and mental (psychiatric) problems.

In the clinical studies with patients using CONCERTA®, the very common side effects (may affect more than 1 in 10 people) were headache, stomach pain, sleeplessness, dry mouth, nausea (feeling sick) and decreased appetite. Other side effects commonly seen with CONCERTA® (may affect up to 1 in 10 people) include vomiting, fast heart rate, weight loss, anxiety, irritability, increased sweating, dizziness, nervousness, tics, increased blood pressure. Tell your doctor if you / your child have blurred vision when taking CONCERTA®.

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

Stimulants may impair your / your child's ability to operate potentially hazardous machinery or vehicles. You should exercise caution until you are reasonably certain that CONCERTA® does not adversely affect your / your child's ability to engage in such activities.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom / effect	Call your doctor right away		Stop taking drug and seek immediate emergency medical assistance
	Only if severe	In all cases	
Very Rare			
Signs of heart problems, such as chest pain, shortness of breath, or fainting		✓	
Convulsions (seizures)			✓
Persistent (greater than 4 hours in duration) and painful erections (priapism)			✓

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom / effect	Call your doctor right away		Stop taking drug and seek immediate emergency medical assistance
	Only if severe	In all cases	
New or worsening psychotic or manic symptoms: -Paranoia, delusions -Hallucinations: seeing, feeling or hearing things that are not real -Mania: feeling unusually excited, over-active, or uninhibited **(see Warnings and Precautions)**		✓	
Suicidal behaviour: Thoughts or actions about hurting or killing yourself. **(see Warnings and Precautions)**			✓
Liver damage or sudden liver failure. Symptoms may include yellowing of the whites of the eyes, or of the skin, dark urine, bleeding, mental clouding (feeling like you're in a fog), confusion.		✓	
Problem with blood vessels in the brain (such as inflamed blood vessels, stroke caused by a burst blood vessel or blocked blood supply to the brain). Symptoms may include severe headaches, weakness or paralysis of any body part, or problems with coordination, vision, speaking, finding words or with your memory.			✓
Rare			
Symptoms of allergic reaction, such as itching, skin rash, swelling of the mouth, face, lips, or tongue, or shortness of breath.			✓
Common			
Aggressive behaviour or hostility		✓	
Unknown			
Raynaud's Phenomenon: discoloration of the fingers and toes, pain, sensations of cold and/or numbness		✓	

This is not a complete list of side effects. For any unexpected effects while taking CONCERTA®, contact your doctor or pharmacist.

HOW TO STORE IT

CONCERTA® should be stored in a safe place at room temperature (between 15-30ºC). Do not store this medicine in hot, damp or humid places.

Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator **1908C**
    Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.

NOTE: Should you require information related to the management of the side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For questions, concerns, or the full Product Monograph go to: www.janssen.com/canada or contact the manufacturer, Janssen Inc., at: 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by
Janssen Inc.
Toronto, Ontario M3C 1L9

Distribution Address:
Markham, Ontario L3R 0T5

Last revised: April 17, 2019