

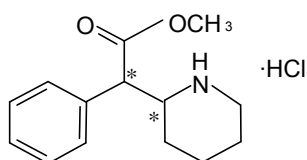
# DATA SHEET

## NAME OF MEDICINE

CONCERTA<sup>®</sup> Extended – Release Tablets  
Methylphenidate hydrochloride

## DESCRIPTION

Methylphenidate hydrochloride is the racemic mixture of d,l methyl  $\alpha$ -phenyl-2-piperidineacetate hydrochloride. The d-isomer is pharmacologically more active than the l-isomer. Methylphenidate hydrochloride is a white, odourless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. It has the following structural formula:



$C_{14}H_{19}NO_2 \cdot HCl$

MW 269.77

CAS-298-59-9 (methylphenidate hydrochloride)

CONCERTA is available as an extended-release tablet for once-a-day oral administration containing 18, 27, 36 or 54 mg methylphenidate hydrochloride. It is designed to have a 12-hour duration of effect.

CONCERTA tablets contain the following inactive ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, Opacode black NS-78-17715, Opadry clear YS-1-19025-A, phosphoric acid, poloxamer, polyethylene oxide, povidone, sodium chloride, stearic acid, succinic acid and synthetic iron oxides. The 18 mg tablet also contains Opadry II yellow YS-30-12788-A. The 27 mg tablet also contains Opadry II grey Y-30-17528. The 36 mg tablet also contains Opadry II white Y-30-18037. The 54 mg tablet also contains Opadry II red Y-30-15567-A.

## PHARMACOLOGY

### Pharmacodynamics

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

### Pharmacokinetics

**Absorption:** Methylphenidate is readily absorbed. Following oral administration of CONCERTA to adults, the drug overcoat dissolves and plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 to 2 hours. The methylphenidate contained in two internal drug layers is gradually released over the next few hours. Peak plasma concentrations are achieved at about 6 to 8 hours after which plasma levels of methylphenidate gradually decrease. CONCERTA once daily minimises the fluctuations between peak and trough concentrations associated with

immediate-release methylphenidate three times daily. The extent of absorption of CONCERTA once daily is generally comparable to conventional immediate release preparations given three times daily.

Following the administration of CONCERTA 18 mg once daily in 36 adults, the mean pharmacokinetic parameters were  $C_{max}$   $3.7 \pm 1.0$  ng/mL,  $T_{max}$   $6.8 \pm 1.8$  h,  $AUC_{\infty}$   $41.8 \pm 13.9$  ngh/mL and  $t_{1/2}$   $3.5 \pm 0.4$  h. No differences in the pharmacokinetics of CONCERTA were noted following single and repeated once daily dosing indicating no significant drug accumulation. The AUC and  $t_{1/2}$  following repeated once daily dosing are similar to those following the first dose of CONCERTA 18 mg.

Following administration of CONCERTA in single doses of 18, 36 and 54 mg/day to adults,  $C_{max}$  and  $AUC_{0-\infty}$  of d-methylphenidate were proportional to dose, whereas l-methylphenidate  $C_{max}$  and  $AUC_{0-\infty}$  increased disproportionately with respect to dose. Following administration of CONCERTA, plasma concentrations of the l-isomer were approximately 1/40th the plasma concentrations of the d-isomer.

In healthy adults, single and multiple dosing of once daily CONCERTA doses from 54 to 144 mg/day resulted in linear and dose proportional increases in  $C_{max}$  and  $AUC_{inf}$  for total methylphenidate (MPH) and its major metabolite, (alpha)-phenyl-piperidine acetic acid (PPAA). The single dose and steady state (Day 4) clearance and half-life parameters were similar, indicating that there was no time dependency in the pharmacokinetics of methylphenidate. The ratio of metabolite (PPAA) to parent drug (MPH) was constant across doses from 54 to 144 mg/day, both after single dose and upon multiple dosing.

Pharmacokinetic equivalence has been demonstrated for two 27-mg CONCERTA tablets with three 18-mg CONCERTA tablets. The mean values of the treatment ratio (2 x 27 mg fasted/3 x 18 mg fasted) of the log-transformed pharmacokinetic values for  $C_{max}$ ,  $T_{max}$  and  $AUC_{inf}$  were 101.1%, 104.3% and 100.3% respectively. The 90% CIs for the treatment ratios were within the pre-specified 80% - 125% range.

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

Studies on the effects of dosing after overnight fasting, after consumption of a normal breakfast and a high-fat breakfast showed no differences in pharmacokinetics or pharmacodynamics of CONCERTA. There is no evidence of dose dumping in the presence or absence of food.

**Distribution:** Plasma methylphenidate concentrations in adults decline biexponentially following oral administration. The terminal plasma half-life of methylphenidate in adults following oral administration of CONCERTA was approximately 3.5 hours.

**Metabolism:** In humans, methylphenidate is metabolised primarily by de-esterification to  $\alpha$ -phenyl-piperidine acetic acid (PPAA) which has little or no pharmacologic activity. In adults the metabolism of CONCERTA once daily, as evaluated by metabolism to PPAA, is similar to that of methylphenidate three times daily. The metabolism of single and repeated once daily doses of CONCERTA is similar.

**Elimination:** After oral dosing of radiolabelled 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. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is not expected to have a significant effect on the pharmacokinetics of CONCERTA.

## CLINICAL TRIALS

### *Children*

CONCERTA was demonstrated to be effective in the treatment of ADHD, in children aged 6 to 12 years, in three pivotal studies. Studies 1 and 2 were single-centre, double-blind, double-dummy, randomised, placebo and active-controlled, crossover comparisons (n = 64 and 70). Study 3 was a multicentre, 4 week, double-blind, double-dummy, randomised, placebo and active-controlled, parallel study (n = 282). The primary comparison of interest in all three trials was CONCERTA versus placebo.

The primary efficacy parameter for CONCERTA was the Inattention/Overactivity with Aggression (IOWA) Conners I/O subscale rated by the community school teacher. Statistically significant ( $p < 0.001$ ) reduction in the Inattention/Overactivity subscale versus placebo was shown consistently across all three controlled studies for CONCERTA once daily.

Onset and duration of efficacy were assessed by the laboratory school teacher using the SKAMP (Swanson, Kotkin, Agler, M-Fynn and Pelham) combined attention ratings for studies 1 and 2. The onset of efficacy was estimated to be 1.5 hours and duration continued through to 12 hours. Patients demonstrated higher productivity and greater accuracy during CONCERTA treatment.

### **Adults**

Two double-blind, placebo-controlled studies were conducted in 627 adults aged 18 to 65 years. The controlled studies compared CONCERTA administered once daily and placebo in a multi-centre, parallel group, 5-week, fixed-dose study (Study 4) (18, 36, and 72 mg/day) and in a multi-centre, parallel group, 7-week dose-titration study (Study 5) (36 to 108 mg/day).

Study 4 was a multi-centre, double-blind, randomized, placebo-controlled, parallel group, dose-response study (5-week duration) with 3 fixed dose groups (18, 36, and 72 mg). Patients were randomized to receive CONCERTA administered at doses of 18 mg ( $n=101$ ), 36 mg ( $n=102$ ), 72 mg/day ( $n=102$ ), or placebo ( $n=96$ ). All three doses of CONCERTA were significantly more effective than placebo in improving CAARS (Conners' Adult ADHD Rating Scale) total scores at double-blind end point in adult subjects with ADHD.

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

## **INDICATIONS**

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

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years.

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

**Long term use:** The effectiveness of CONCERTA for long-term use has not been systematically evaluated in controlled trials. Therefore the physician who elects to use CONCERTA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

## **CONTRAINDICATIONS**

CONCERTA is contraindicated:

- in patients with known hypersensitivity to methylphenidate or any inactive ingredient used in this product (see **DESCRIPTION**);

- in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms;
- in patients with glaucoma;
- in patients with a family history or diagnosis of Tourette's syndrome;
- 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);
- in patients with hyperthyroidism;
- .
- Pheochromocytoma
- Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder.
- Diagnosis or history of severe and episodic (Type I) Bipolar (affective) Disorder (that is not well-controlled)
- pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels).
- pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke

## PRECAUTIONS

### Use with caution in the following circumstances

**Depression and Psychosis:** CONCERTA should not be used to treat severe depression or for the prevention or treatment of normal fatigue states.

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, methylphenidate should not be given unless the benefits outweigh the risks to the patient.

Development or worsening of psychiatric disorders should be monitored at every adjustment of dose, then at least every 6 months, and at every visit; discontinuation of treatment may be appropriate.

In psychotic patients administration of methylphenidate may exacerbate symptoms of behaviour disturbance and thought disorder.

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking or mania in patients 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.

**Suicidal tendency:** Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Consideration should be given to the exacerbation of an underlying psychiatric condition and to a possible causal role of methylphenidate treatment. Treatment of an underlying psychiatric condition may be necessary and consideration should be given to a possible discontinuation of methylphenidate.

**Forms of bipolar disorder:** Particular care should be taken in using methylphenidate to treat ADHD in patients with comorbid bipolar disorder (including untreated Type I Bipolar Disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such

patients. Prior to initiating treatment with methylphenidate, 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. Close ongoing monitoring is essential in these patients (see **Depression and Psychosis** above and **DOSAGE AND ADMINISTRATION**). Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.

**Tics:** Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of methylphenidate. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate. Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.

**Drug Dependence:** Patients should be carefully monitored for the risk of diversion, misuse and abuse of methylphenidate. CONCERTA should be given cautiously to patients with a history of drug or alcohol dependence. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour.

Patient age, the presence of risk factors for substance use disorder (such as co-morbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should all be taken into account when deciding on a course of treatment for ADHD. Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because such patients may increase the dosage on their own initiative.

For some high-risk substance abuse patients, methylphenidate or other stimulants may not be suitable and non-stimulant treatment should be considered.

Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

**Drug Screening:** CONCERTA contains methylphenidate which may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test.

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

**Potential for Gastrointestinal Obstruction:** CONCERTA tablet is non-deformable and does not appreciably change in shape in the GIT. It should not ordinarily be administered to patients with pre-existing severe GI narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. Due to the prolonged-release design of the tablet, CONCERTA should only be used in patients who are able to swallow the tablet whole.

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

## **Sudden Death and Pre-existing Structural Cardiac Abnormalities**

Although a causal relationship has not been established, sudden death has been reported in patients with structural cardiac abnormalities treated with ADHD drugs with stimulant effects. These treatments should be used with caution in patients with structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

## Hypertension and Cardiovascular Conditions

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

In the laboratory clinical trials in children both CONCERTA and methylphenidate three times daily increased resting pulse by an average of 2 to 6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1 to 4 mm Hg during the day, relative to placebo. In placebo-controlled studies in adults, mean increases in resting pulse rate of approximately 4 to 6 bpm were observed with CONCERTA at endpoint vs. a mean change of roughly -2 to 3 bpm with placebo. Mean changes in blood pressure at endpoint ranged from about -1 to 1 mm Hg (systolic) and 0 to 1 mm Hg (diastolic) for CONCERTA and from -1 to 1 mm Hg (systolic) and -2 to 0 mm Hg (diastolic) for placebo. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate.

Cardiovascular status should be carefully monitored. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months.

The use of methylphenidate is contraindicated in certain pre-existing cardiovascular disorders unless specialist paediatric cardiac advice has been obtained

**Misuse and Cardiovascular Events:** Misuse of stimulants of the central nervous system may be associated with sudden death and other serious cardiovascular adverse events.

**Cerebrovascular disorders:** See **CONTRAINDICATIONS** for cerebrovascular conditions in which methylphenidate treatment is contraindicated. Patients with additional risk factors (such as a history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with methylphenidate.

Cerebral vasculitis appears to be a very rare idiosyncratic reaction to methylphenidate exposure. There is little evidence to suggest that patients at higher risk can be identified and the initial onset of symptoms may be the first indication of an underlying clinical problem. Early diagnosis, based on a high index of suspicion, may allow the prompt withdrawal of methylphenidate and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during methylphenidate therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory..

Treatment with methylphenidate is not contraindicated in patients with hemiplegic cerebral palsy.

## Aggression

Aggressive behaviour or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behaviour or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes.

## Haematologic Monitoring

Periodic full blood count, differential and platelet counts are advised during prolonged therapy.

## Use in patients with renal impairment

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

## Use in patients with hepatic impairment

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

## Use in children

The safety and efficacy of CONCERTA in children under 6 years old have not been established.

**Long-term use (more than 12 months) in children and adolescents:** The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance under DOSAGE AND ADMINISTRATION and PRECAUTIONS for hypertension and cardiovascular conditions, growth, appetite, development of *de novo* or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below, and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration.

The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferably during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

**Growth:** Moderately reduced weight gain and growth retardation have been reported with the long-term use of methylphenidate in children.

The effects of methylphenidate on final height and final weight are currently unknown and being studied.

Growth should be monitored during methylphenidate treatment: height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

**Use in the elderly:** Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group.

## Carcinogenicity, mutagenicity, impairment of fertility

In a lifetime dietary carcinogenicity study carried out in mice, methylphenidate caused an increase in hepatocellular adenomas at a dose of 60–80 mg/kg/day, and in males only, an increase in hepatoblastomas (a relatively rare rodent malignant tumour type) at 60 mg/kg/day. These dose levels are approximately 3–8 fold the maximal recommended clinical dose on a mg/m<sup>2</sup> basis. There was no increase in tumours at 30–40 mg/kg/day (approximately 1-4 fold the maximal recommended clinical dose on a mg/m<sup>2</sup> basis). The mouse strain used is sensitive to the development of hepatic tumours, and the significance of these results to humans is not known. There was no evidence of carcinogenicity in two strains of transgenic mice administered methylphenidate in the diet for 24 weeks at doses up to 60–74 mg/kg/day (approximately 3–8 fold the maximal recommended clinical dose on a

mg/m<sup>2</sup> basis) or in a lifetime dietary study in rats at doses up to 50 mg/kg/day (approximately 4–10 fold the maximal recommended clinical dose on a mg/m<sup>2</sup> basis).

Methylphenidate was not mutagenic in the *in vitro* assays (Ames reverse mutation assay, mouse lymphoma cell forward mutation assay). Methylphenidate was weakly clastogenic *in vitro* (Chinese Hamster ovary cells) but was negative *in vivo* (mouse bone marrow micronucleus assay). Sister chromatid exchange assay results were positive only at high (cytotoxic) concentrations.

Dietary administration of methylphenidate to male and female mice at doses up to 150–160 mg/kg/day did not impair fertility in an 18–week continuous breeding study in which both parents and offspring were treated. This dose was approximately 7–16 fold the maximal recommended human dose on a mg/m<sup>2</sup> basis.

## Use in pregnancy

### Category B3

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

There is a limited amount of data from the use of methylphenidate in pregnant women.

Cases of neonatal cardiorespiratory toxicity, specifically fetal tachycardia and respiratory distress have been reported in spontaneous case reports.

Oral administration of methylphenidate to rabbits during the period of organogenesis has produced teratogenic effects at doses of 200 mg/kg/day, associated with systemic exposure (plasma AUC) approximately 5-6 fold that in humans receiving the maximal recommended dose. The exposure at the no-effect dose in rabbits (60 mg/kg/day) was less than human exposure. Teratogenic effects were not seen in rats at oral methylphenidate doses up to 75 mg/kg/day, associated with systemic exposure of 21-25 fold that in humans receiving the maximal dose. Oral administration of methylphenidate to rats from early pregnancy until weaning was associated with maternal toxicity, reduced offspring weight and marginal alterations in neuromotor performance in offspring at a maternal dose of 30 mg/kg/day, approximately 3-6 fold the maximum recommended clinical dose on a mg/m<sup>2</sup> basis.

## Use in lactation

Methylphenidate has been found in the breast-milk of a woman treated with methylphenidate

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.

Oral administration of methylphenidate to rats from early pregnancy until weaning was associated with maternal toxicity, reduced offspring weight and marginal alterations in neuromotor performance in offspring at a maternal dose of 30 mg/kg/day, approximately 3-6 fold the maximum recommended clinical dose on a mg/m<sup>2</sup> basis.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from methylphenidate therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

## Interactions with other drugs

### Pharmacokinetic interaction:

It is not known how methylphenidate may effect plasma concentrations of concomitantly administered drugs. Therefore, caution is recommended at combining methylphenidate with other drugs, especially those with a narrow therapeutic window.

Methylphenidate is not metabolised by cytochrome P450 to a clinically relevant extent. Inducers or inhibitors of cytochrome P450 are not expected to have any relevant impact on methylphenidate

pharmacokinetics. Conversely, the d- and l- enantiomers of methylphenidate do not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

However, there are reports indicating that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, phenytoin, primidone) and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

### **Pharmacodynamic interactions:**

#### **Anti-hypertensive drugs**

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

#### **Use with drugs that elevate blood pressure**

Caution is advised in patients being treated with methylphenidate with any other drug that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in Section 4.4 Warnings and Precautions for use)

Because of possible hypertensive crisis, methylphenidate is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors (see section 4.3 Contraindications).

#### **Use with alcohol**

Alcohol may exacerbate the adverse CNS effects of psychoactive drugs, including methylphenidate. It is therefore advisable for patients to abstain from alcohol during treatment.

#### **Use with halogenated anaesthetics**

There is a risk of sudden blood pressure increase during surgery. If surgery is planned, methylphenidate treatment should not be used on the day of surgery.

#### **Use with dopaminergic drugs**

Caution is recommended when administering methylphenidate with dopaminergic drugs, including antipsychotics. Because a predominant action of methylphenidate is to increase extracellular dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

### **Effect on ability to drive or operate machinery**

Methylphenidate can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision and 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.

### **Instructions to the patient**

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

## **ADVERSE EFFECTS**

## Clinical Trial Data

### Double-Blind Data – Adverse Drug Reactions Reported at ≥1% Frequency

Adverse Drug Reactions (ADRs) in either the paediatric or adult double-blind studies (**Table 1 and 2**) may be relevant for both patient populations.

#### Paediatric Patients

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

Adverse Drug Reactions (ADRs) reported by ≥1% of CONCERTA-treated children and adolescent subjects and more frequently than placebo in these trials are shown in **Table 1**.

<b>Table 1. Adverse Drug Reactions Reported by ≥1% of CONCERTA-Treated Children and Adolescent Subjects and More Frequently than Placebo in 4 Placebo-Controlled, Double-Blind Clinical Trials</b>		
<b>System/Organ Class</b> Adverse Drug Reaction	<b>CONCERTA</b> <b>(n=321)</b> %	<b>Placebo</b> <b>(n=318)</b> %
<b>Infections and Infestations</b>		
Nasopharyngitis	2.8	2.2
<b>Psychiatric Disorders</b>		
Insomnia	2.8	0.3
<b>Nervous System Disorders</b>		
Headache	10.6	11.9
Dizziness	1.9	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Cough	1.9	0.9
Oropharyngeal Pain	1.2	0.9
<b>Gastrointestinal Disorders</b>		
Abdominal Pain upper	6.2	3.8
Vomiting	2.8	1.6
<b>General Disorders and Administration Site Conditions</b>		
Pyrexia	2.2	0.9

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

The majority of ADRs were mild to moderate in severity.

#### Adult Patients

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

Adverse Drug Reactions (ADRs) reported by ≥1% of CONCERTA-treated adult subjects in these trials are shown in **Table 2**.

<b>Table 2. Adverse Drug Reactions Reported by ≥1% of CONCERTA-Treated Adult Subjects in 3 Placebo-Controlled, Double-Blind Clinical Trials</b>		
<b>System/Organ Class</b> Adverse Drug Reaction	<b>CONCERTA</b> <b>(n=596)</b> %	<b>Placebo</b> <b>(n=309)</b> %
<b>Infections and Infestations</b>		
Upper respiratory tract infection	1.7	1.0
Sinusitis	1.3	1.0
<b>Metabolism and Nutrition Disorders</b>		
Decreased appetite	24.8	6.1
Anorexia	4.2	1.3
<b>Psychiatric Disorders</b>		
Insomnia	13.3	7.8
Anxiety	8.4	2.9
Initial insomnia	5.7	2.6
Depressed mood	4.4	2.6
Restlessness	4.0	0
Agitation	3.2	0.6
Nervousness	2.3	0.6
Bruxism	1.5	0.6
Depression	1.5	0.6
Affect lability	1.3	0.6
Libido decreased	1.3	0.6
Panic attack	1.3	0.3
Tension	1.3	0.3
Aggression	1.2	0.6
Confusional state	1.0	0.3
<b>Nervous System Disorders</b>		
Headache	24.2	18.8
Dizziness	7.4	5.5
Tremor	3.4	0.6
Paresthesia	1.2	0
Tension headache	1.0	0.3
<b>Eye Disorders</b>		
Accommodation disorder	1.3	0
Vision blurred	1.3	1.0
<b>Ear and Labyrinth Disorders</b>		
Vertigo	2.0	0.3
<b>Cardiac Disorders</b>		
Tachycardia	6.0	0
Palpitations	4.5	0.6
<b>Vascular Disorders</b>		
Hypertension	2.2	1.6
Hot flush	1.3	0.6
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Oropharyngeal pain	1.5	1.3
Cough	1.2	1.0
Dyspnoea	1.2	0.6
<b>Gastrointestinal Disorders</b>		
Dry mouth	15.1	3.6
Nausea	14.3	4.9
Dyspepsia	2.0	1.9
Vomiting	1.8	0.6
Constipation	1.5	0.6
<b>Skin and Subcutaneous Tissue Disorders</b>		
Hyperhidrosis	5.7	1.3
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Muscle tightness	1.3	0

Muscle spasms	1.0	0.3
<b>Reproductive System and Breast Disorders</b>		
Erectile dysfunction	1.0	0.3
<b>General Disorders and Administration Site Conditions</b>		
Irritability	5.2	2.9
Fatigue	4.7	4.2
Thirst	1.8	0.6
Asthenia	1.2	0
<b>Investigations</b>		
Weight decreased	8.7	3.6
Heart rate increased	3.0	1.9
Blood pressure increased	2.5	1.9
Alanine aminotransferase increased	1.0	0

The majority of ADRs were mild to moderate in severity.

**Open-Label Data – Adverse Drug Reactions Reported at ≥1% Frequency**

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

Adverse Drug Reactions (ADRs) reported by ≥1% of CONCERTA-treated subjects in these trials and not listed in **Table 1 and 2** are shown in **Table 3**

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

The majority of ADRs were mild to moderate in severity.

**Double Blind and Open-Label Data – Adverse Drug Reactions Reported at <1% Frequency**

Additional ADRs that occurred in <1% of CONCERTA-treated paediatric and adult subjects in the double-blind and open-label clinical datasets are listed in **Table 4**.

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

The majority of ADRs were mild to moderate in severity.

**Postmarketing Data**

ADRs identified during postmarketing experience with CONCERTA are included in **Table 5**. 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

<b>Table 5. Adverse Drug Reactions Identified During Postmarketing Experience with CONCERTA by Frequency Category Estimated from Spontaneous Reporting Rates</b>	
<b>Blood and Lymphatic System Disorders</b>	
<i>Very rare</i>	Pancytopenia, Thrombocytopenia, Thrombocytopenic Purpura
<b>Immune System Disorders</b>	
<i>Rare</i>	Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions and Exanthemas NEC
<b>Psychiatric Disorders</b>	
<i>Very rare</i>	Disorientation, Hallucination, Hallucination Auditory, Hallucination Visual, Mania
<b>Nervous System Disorders</b>	
<i>Very rare</i>	Convulsion, Grand Mal Convulsion, Dyskinesia
<b>Eye Disorders</b>	
<i>Very rare</i>	Diplopia, Mydriasis, Visual Impairment
<b>Cardiac Disorders</b>	
<i>Very rare</i>	Angina Pectoris, Bradycardia, Extrasystoles, Supraventricular Tachycardia, Ventricular Extrasystoles
<b>Vascular Disorders</b>	
<i>Very rare</i>	Raynaud's Phenomenon
<b>Skin and Subcutaneous Tissue Disorders</b>	
<i>Very rare</i>	Alopecia, Erythema
<b>Musculoskeletal, and Connective Tissue Disorders</b>	
<i>Very rare</i>	Arthralgia, Myalgia, Muscle Twitching
<b>General Disorders and Administration Site Conditions</b>	
<i>Rare</i>	Therapeutic Response Decreased
<i>Very rare</i>	Chest Pain, Chest Discomfort, Drug Effect Decreased, Hyperpyrexia
<b>Investigations</b>	
<i>Very rare</i>	Blood Alkaline Phosphatase Increased, Blood Bilirubin Increased, Hepatic Enzyme Increased, Platelet Count Decreased, White Blood Cell Count Abnormal

## DOSAGE AND ADMINISTRATION

CONCERTA is administered orally once daily and should be taken in the morning.

CONCERTA must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

CONCERTA may be administered with or without food.

### Pre-treatment screening:

Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate. A comprehensive history should document concomitant medications, past and present co-morbid medical and psychiatric disorders or

symptoms, family history of sudden cardiac/unexplained death and accurate recording of pre-treatment height and weight on a growth chart (see CONTRAINDICATIONS and PRECAUTIONS)

**Ongoing monitoring:**

Growth, psychiatric and cardiovascular status should be continuously monitored (see also PRECAUTIONS).

- Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months;
- height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart;
- development of *de novo* or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then least every 6 months and at every visit.

Patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate.

**Dose titration:**

Careful dose titration is necessary at the start of treatment with methylphenidate. Dose titration should be started at the lowest possible dose.

**Children (over 6 years of age) and adolescents:**

Dosage may be adjusted in 9 mg increments between 18 mg and 36mg and consecutively in 18 mg increments to a maximum of 54 mg/day for children aged between 6-12 years and to a maximum of 72 mg/day for adolescents aged between 13-18 years. In general, dosage adjustment may proceed at approximately weekly intervals.

**Adults:**

Dosage can be adjusted from an initial dose of 18 or 36 mg/day in 18mg increments to a maximum of 72mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

Patients respond at different dose levels and CONCERTA must be titrated to effect on an individual patient needs and response basis. A maximum dose of 108 mg/day have been included in clinical trials (see CLINICAL TRIALS).

**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 children and adolescents and 18 or 36 mg once daily for adults.

**Patients Currently Using Methylphenidate:** The recommended dose of CONCERTA for patients who are currently taking methylphenidate two or three times daily at doses of 10 – 60 mg per day is provided in **Table 6**.

**Table 6: Recommended dose conversions from methylphenidate regimens to CONCERTA**

Previous methylphenidate daily dose	Recommended CONCERTA starting dose
5 mg methylphenidate three times daily	18 mg every morning
10 mg methylphenidate three times daily	36 mg every morning
15 mg methylphenidate three times daily	54 mg every morning
20 mg methylphenidate three times daily	72 mg every morning

Clinical judgement should be used when selecting the dose for patients currently taking methylphenidate in other regimens. Daily dosage above 54 mg is not recommended for children aged between 6-12 years. Daily dosage above 72 mg is not recommended for adolescents aged between 13-18 years.

**Long-term (more than 12 months) use in children and adolescents:**

The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite.

Methylphenidate treatment is usually discontinued during or after puberty. The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferable during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

**Dose reduction and discontinuation:**

Treatment must be stopped if the symptoms do not improve after appropriate dosage adjustment over a one-month period. If paradoxical aggravation of symptoms or other serious adverse events occur, the dosage should be reduced or discontinued.

## **Use in Infants and children**

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

## **Use in Elderly**

Use of CONCERTA in patients over 65 years of age has not been studied in controlled trials.

## **OVERDOSAGE**

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

## **Signs and Symptoms**

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

## **Treatment**

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for pyrexia.

Efficacy of peritoneal dialysis or extracorporeal haemodialysis for CONCERTA overdose has not been established.

## **PRESENTATION**

CONCERTA 18 mg are yellow capsule-shaped tablets, with "alza 18" printed in black ink on one side.  
CONCERTA 36 mg are white capsule-shaped tablets, with "alza 36" printed in black ink on one side.  
CONCERTA 27 mg are grey capsule-shaped tablets, with "alza 27" printed in black ink on one side.  
CONCERTA 54 mg are brownish-red capsule-shaped tablets, with "alza 54" printed in black ink on one side.  
CONCERTA tablets are supplied in HDPE bottles of 30 containing silica gel desiccant.

## **MEDICINE CLASSIFICATION**

Controlled Drug – B2

## **STORAGE**

Store below 25°C. Keep container tightly closed.

## **SHELF LIFE**

3 years

## **NAME AND ADDRESS**

### **New Zealand Sponsor**

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