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# CONCERTA®

## DATA SHEET

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### 1. PRODUCT NAME

CONCERTA® Extended – Release Tablets 18 mg methylphenidate hydrochloride modified release tablet

CONCERTA® Extended – Release Tablets 27 mg methylphenidate hydrochloride modified release tablet

CONCERTA® Extended – Release Tablets 36 mg methylphenidate hydrochloride modified release tablet

CONCERTA® Extended – Release Tablets 54 mg methylphenidate hydrochloride modified release tablet

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One extended release tablet contains 18 mg, 27 mg, 36 mg or 54 mg of methylphenidate hydrochloride.

Excipient(s) with known effect:

Lactose

For the full list of excipients, see **section 6.1 List of excipients**.

### 3. PHARMACEUTICAL FORM

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 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.

### 4. CLINICAL PARTICULARS

#### 4.1. Therapeutic 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.

## 4.2. Dose and method of 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 **section 4.3 Contraindications** and **section 4.4 Special warnings and precautions for use**).

### Ongoing monitoring:

Growth, psychiatric and cardiovascular status should be continuously monitored (see also **section 4.4 Special warnings and precautions for use**).

- 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.

### 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 1**.

**Table 1: Recommended dose conversions from methylphenidate regimens to CONCERTA**

<b>Previous methylphenidate daily dose</b>	<b>Recommended CONCERTA starting dose</b>
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.

**Special Populations**

*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.

**Method of administration**

CONCERTA must be swallowed whole with the aid of liquids.

Tablets should not be chewed, divided or crushed.

The medication is contained within a 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.

**4.3. Contraindications**

CONCERTA is contraindicated:

- in patients with known hypersensitivity to methylphenidate or any inactive ingredient used in this product (see **section 6.1 List of excipients**);
- 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.

#### 4.4. Special warnings and precautions for use

##### 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 **section 4.2 Dose and method of administration**). Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.

### **Tics and worsening of Tourette's syndrome**

Methylphenidate is 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.

### **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.

### **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.

### **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 **section 4.3 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.

### **Priapism**

Prolonged and painful erections requiring immediate medical attention (sometimes including surgical intervention, have been reported with methylphenidate products, including CONCERTA, in both paediatric and adult patients (see **section 4.8 Undesirable effects**). 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.

### **Cerebrovascular disorders**

Cerebrovascular disorders (including cerebral vasculitis and cerebral hemorrhage) have been reported with the use of CONCERTA (see **section 4.8 Undesirable effects**). Consider cerebrovascular disorders as a possible diagnosis in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during CONCERTA therapy. These symptoms could include severe headache, unilateral weakness or paralysis, and impairment of coordination, vision, speech, language, or memory. If a cerebrovascular disorder is suspected during treatment, discontinue CONCERTA immediately. Early diagnosis may guide subsequent treatment.

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

### **Aggression, anxiety and agitation**

Aggressive behaviour, marked anxiety, or agitation are often observed in patients with ADHD, and have been reported in patients treated with CONCERTA (see **section 4.8 Undesirable effects**). 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.

## Haematologic Monitoring

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

## Increased intraocular pressure and glaucoma

There have been reports of a transient elevation of intraocular pressure (IOP) associated with methylphenidate treatment. It is recommended to prescribe CONCERTA to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Patients with a history of abnormally increased IOP or open-angle glaucoma, and patients at risk for acute angle-closure glaucoma (e.g., patients with significant hyperopia) must be closely monitored.

CONCERTA is not recommended in patients with acute angle-closure glaucoma.

## 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 **section 4.2 Dose and method of administration** and **section 4.4 Special warnings and precautions for use** 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.

## 4.5. Interactions with other medicines and other forms of interaction

### 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.

### Pharmacodynamic interactions:

#### *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 Special 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**).

#### *Anti-hypertensive drugs*

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension. It is recommended to monitor blood pressure and adjust the dosage of the antihypertensive drug as needed (see **section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

#### *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*

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

#### *Use with 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.

#### *Use with antipsychotic drugs*

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.

#### **4.6. Fertility, pregnancy and lactation**

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

Medicines should only be prescribed in pregnancy when the expected benefits to the mother outweigh any potential risks to the mother and foetus. If possible, medicines should be used at the lowest effective dose for the shortest possible duration. Careful consideration and discussion of the risks and benefits of the medicines should be taken in the management of pregnant women or women intending to become pregnant. Women of child-bearing potential should be fully informed of the risks and benefits of the use of methylphenidate during pregnancy.

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.

##### **Breast-feeding**

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

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.

#### 4.7. 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.

#### 4.8. Undesirable effects

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of methylphenidate based on the comprehensive assessment of the available adverse event information. A causal relationship with methylphenidate cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

#### Clinical Trial Data

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

Adverse Drug Reactions (ADRs) in either the paediatric or adult double-blind studies (**Table 2 and Table 3**) 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 2**.

<b>Table 2. 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 Adverse Drug Reaction</b>	<b>CONCERTA (n=321) %</b>	<b>Placebo (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  $\geq 1\%$  of CONCERTA-treated adult subjects in these trials are shown in **Table 3**.

<b>Table 3. Adverse Drug Reactions Reported by <math>\geq 1\%</math> 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>%</b>	<b>Placebo</b> <b>(n=309)</b> <b>%</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*	1.5	0.6
Panic attack	1.3	0.3
Tension	1.3	0.3
Aggression	1.2	0.6
Confusional state	1.0	0.3
<b>Nervous System Disorders</b>		
Headache	24.2	18.8
Dizziness	7.4	5.5
Tremor	3.4	0.6
Paraesthesia	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>System/Organ Class</b> Adverse Drug Reaction	<b>CONCERTA</b> <b>(n=596)</b> %	<b>Placebo</b> <b>(n=309)</b> %
<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
Investigations		
Weight decreased	8.7	3.6
Heart rate increased	3.0	1.9
Blood pressure increased	2.5	1.9
Alanine aminotransferase increased	1.0	0

\*The adverse reaction libido decreased includes the preferred term loss of libido

The majority of 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 2** and **Table 3** are shown in **Table 4**.

<b>System/Organ Class</b> Adverse Drug Reaction	<b>CONCERTA</b> <b>(n=3782)</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 5**.

<b>Table 5. Adverse Drug Reactions Reported by &lt;1% of CONCERTA-Treated Pediatric and Adult Subjects in Either Double-Blind or Open-Label Clinical Trials</b>	
<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 6**. The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1000 and <1/100
Rare	≥1/10000 and <1/1000
Very rare	<1/10000, including isolated reports

<b>Table 6. 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, Logorrhoea, libido disorder*
<b>Nervous System Disorders</b>	
<i>Very rare</i>	Convulsion, Grand Mal Convulsion, Dyskinesia, Cerebrovascular disorder (including cerebral vasculitis, cerebral haemorrhage, cerebral arteritis, cerebral vascular occlusion)
<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>Respiratory, thoracic and mediastinal disorders</b>	
<i>Very rare</i>	Epistaxis
<b>Skin and Subcutaneous Tissue Disorders</b>	
<i>Very rare</i>	Alopecia, Erythema
<b>Hepatobiliary Disorders</b>	
<i>Very rare</i>	Hepatocellular injury, Acute hepatic failure
<b>Musculoskeletal, and Connective Tissue Disorders</b>	
<i>Very rare</i>	Arthralgia, Myalgia, Muscle Twitching
<b>Reproductive System and Breast Disorders</b>	
<i>Very rare</i>	Priapism
<i>Very rare</i>	Gynecomastia
<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

NEC = not elsewhere classified

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

## 4.9. Overdose

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

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

### Treatment

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

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: centrally acting sympathomimetics: ACT code: N06BA04

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.

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.

## 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.

## 5.2. Pharmacokinetic properties

### 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  $AUC_{\text{inf}}$  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  $AUC_{\text{inf}}$  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  $AUC_{\text{TAU}}$  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.

## **5.3. Preclinical safety data**

### **Carcinogenicity**

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).



## Mutagenicity

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.

## Impairment of fertility

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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

#### Tablet core

- Butylated hydroxytoluene
- Cellulose acetate
- Hypromellose
- Iron oxide black
- Iron oxide red (27 mg & 54 mg only)
- Iron oxide yellow
- Phosphoric acid
- Poloxamer
- Polyethylene oxide
- Povidone
- Sodium chloride
- Stearic acid
- Succinic acid

#### Tablet coating

- Carnauba wax
- OPACODE WB monogramming ink NS-78-17715 BLACK (also contains propylene glycol)
- OPADRY complete film coating system YS-1-19025-A – CLEAR (also contains macrogol 400)
- 18 mg: OPADRY II complete film coating system YS-30-12788-A YELLOW
- 27 mg: OPADRY II complete film coating system Y-30-17528 GRAY
- 36 mg: Opadry II White Y-30-18037
- 54 mg: OPADRY II complete film coating system Y-30-15567-A RED  
(OPADRY II coating systems also contain lactose monohydrate, titanium dioxide and triacetin)

### 6.2. Incompatibilities

Not applicable

### **6.3. Shelf life**

18 mg, 36 mg, 54 mg: 3 years

27 mg: 2 years

### **6.4. Special precautions for storage**

Store below 25°C. Keep container tightly closed.

### **6.5. Nature and contents of container**

CONCERTA tablets are supplied in HDPE bottles containing silica gel desiccant.

Pack sizes: 28, 30, 56, 60 and 100 tablets

Not all pack sizes may be marketed

### **6.6. Special precautions for disposal and other handling**

No special requirements

## **7. MEDICINE SCHEDULE**

Controlled Drug – B2

## **8. SPONSOR**

Janssen-Cilag (New Zealand) Ltd

Auckland, NEW ZEALAND

Telephone: 0800 800 806

## **9. DATE OF FIRST APPROVAL**

14 August 2003 (18 mg, 36 mg & 54 mg)

19 November 2007 (27 mg)

## **10. DATE OF REVISION OF THE TEXT**

16 May 2023

OROS<sup>®</sup> formulation is a trademark of ALZA Corporation

### **Summary table of changes:**

<b>Section changes</b>	<b>Summary of new information</b>
4.8	Add gynecomastia as Adverse Drug Reaction