PROFESSIONAL INFORMATION INSERT

SCHEDULING STATUS

Schedule 6

1. NAME OF THE MEDICINE

CONCERTA® 18 mg (extended-release tablets)

CONCERTA® 27 mg (extended-release tablets)

CONCERTA® 36 mg (extended-release tablets)

CONCERTA® 54 mg (extended-release tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Extended-release tablets containing 18 mg, 27 mg, 36 mg or 54 mg of methylphenidate hydrochloride.

Excipient with known effect

Contains sugar (lactose monohydrate)

Each CONCERTA 18 mg tablet contains 6.49 mg lactose monohydrate

Each CONCERTA 27 mg tablet contains 4.94 mg lactose monohydrate

Each CONCERTA 36 mg tablet contains 14.44 mg lactose monohydrate

Each CONCERTA 54 mg tablet contains 7,6 mg lactose monohydrate

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Extended-release tablets

18 mg: capsule-shaped yellow tablet with “alza 18” printed on one side in black ink.

27 mg: capsule-shaped grey tablet with “alza 27” printed on one side in black ink.

36 mg: capsule-shaped white tablet with “alza 36” printed on one side in black ink.

54 mg: capsule-shaped brownish-red tablet with “alza 54” printed on one side in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CONCERTA is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents aged 6-17 and adults aged 18 to 65 who meet DSM-IV criteria for ADHD.

4.2 Posology and method of administration

Posology

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 three times daily at doses of 15 to 60 mg/day is provided in Table 1. Dosing recommendations are based on current dose regimen and clinical judgement.

Table 1. Recommended Dose Conversion from Other Methylphenidate Regimens to CONCERTA

Previous Methylphenidate Daily Dose	Recommended CONCERTA Dose
5 mg Methylphenidate hydrochloride twice daily or three times daily.	18 mg once daily
10 mg Methylphenidate hydrochloride twice daily or three times daily	36 mg once daily
15 mg Methylphenidate hydrochloride twice daily or three times daily.	54 mg once daily
20 mg Methylphenidate hydrochloride twice daily or three times daily	72 mg once daily

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

Dosage may be adjusted 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 for adolescents aged between 13 – 18 years and 108 mg in adults. In general, dosage adjustment may proceed at approximately weekly intervals.

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.

Daily dosage above 108 mg is not recommended in adults.

Maintenance/Extended Treatment:

The long-term use of CONCERTA has not been systematically evaluated in controlled clinical trials. The physician who elects to use CONCERTA for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the medicine for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy.

Changing from one extended-release methylphenidate product to another

The efficacy and tolerability profile of CONCERTA over the dosing period is determined by the specific release profile of the product. Other extended-release methylphenidate formulations with different release profiles may have different efficacy and tolerability profiles. If changing from one extended-release methylphenidate product to another, it is recommended that this be carried out only with additional medical supervision.

Dose reduction and discontinuation:

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, CONCERTA should be discontinued.

Special populations

Elderly:

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

Method of administration

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

CONCERTA may be administered with or without food.

Dosage should be individualized according to the need and response of each individual patient.

CONCERTA should not be used in patients under six years old.

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

4.3 Contraindications

CONCERTA is contraindicated:

- in patients known to be hypersensitive to methylphenidate or other components of CONCERTA;
- in patients with poorly controlled open-angle or angle-closure glaucoma;
- during treatment with monoamine oxidase inhibitors, and within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (as hypertensive crises may result);
- in patients with hyperthyroidism, cardiac dysrrhythmias, ischaemic heart disease, uncontrolled hypertension;

- in pregnancy and lactation. (see section 4.6)

4.4 Special warnings and precautions for use

CONCERTA increases heart rate, systolic and diastolic blood pressure, therefore caution is advised when CONCERTA is prescribed for ADHD patients whose underlying medical conditions might be compromised by increases in heart rate and/or blood pressure e.g. heart failure and hypertension. Blood pressure should be monitored in patients treated with CONCERTA especially those with hypertension (see section 4.3).

Structural cardiac abnormalities

Cases of sudden death have been reported in ADHD patients with structural cardiac abnormalities treated with CONCERTA used, at usual doses. Although the data are inconclusive regarding causal relationship between treatment with CONCERTA and sudden death, caution is advised when CONCERTA, is prescribed for ADHD patients with structural cardiac abnormalities.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take CONCERTA.

Patients under 6 years old

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

Motor and verbal tics, and worsening of Tourettes's syndrome

CONCERTA has been associated with the onset or exacerbation of motor and verbal tics. Worsening of verbal 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

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

Long-term use

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

Increased intraocular pressure and glaucoma

There have been reports of 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 glaucoma.

CONCERTA is contraindicated in all patients with poorly controlled glaucoma (see section 4.3).

Dose administration

CONCERTA must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided or crushed. Methylphenidate is contained within a nonabsorbable shell designed to release the medicine at an extended 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 stools something that looks like a tablet.

Because the CONCERTA tablet is non-deformable and does not appreciably change in shape in the GI tract, CONCERTA should not be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been reports of obstructive symptoms in patients with known strictures. Due to the extended-release design of the tablet, CONCERTA should only be used in patients who are able to swallow the tablet whole.

Use in other indications

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

Psychotic or manic symptoms

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

Aggression, anxiety and agitation

Aggressive behaviour, marked anxiety, or agitation are often observed with patients with ADHD, and have been reported in patients treated with CONCERTA (see section 4.8). Anxiety led to discontinuation of CONCERTA is some patients. It is recommended to monitor patients beginning treatment with CONCERTA for appearance of, or worsening of, aggressive behaviour, marked anxiety, or agitation and at every adjustment of dose and then at least every 6 months or every visit.

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). 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 haemorrhage) have been reported with the use of CONCERTA (see section 4.8). 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.

Conditions requiring caution

CONCERTA should be given with caution in the following conditions:

- ***Psychotic patients:*** Administration of CONCERTA may exacerbate symptoms of behaviour disturbances and thought disorder in psychotic patients.
- ***Underlying medical conditions that might be compromised by increases in blood pressure or heart rate*:** In clinical trials in children, CONCERTA increased resting pulse by an average of 2-6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1-4 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. (see section 4.4)

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

Hematologic monitoring

Periodic haematologic monitoring (Complete blood count, differential, and platelet counts) is advised during prolonged therapy.

Lactose

Contains lactose which may an effect on the glycaemic control of patients with diabetes mellitus.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take CONCERTA.

4.5 Interaction with other medicinal products and other forms of interaction

Because of the effects on blood pressure, CONCERTA should be used cautiously with pressor agents.

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

Human pharmacological studies have shown that methylphenidate may inhibit the metabolism of warfarin anticoagulants, anticonvulsants (e.g. phenobarbital,

phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors).

Downward dose adjustment of these medicines may be required when given concomitantly with CONCERTA. It may be necessary to adjust the dosage and monitor plasma medicines concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant use of CONCERTA.

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

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using CONCERTA in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Alcohol may exacerbate the adverse CNS effects of CONCERTA. It is therefore desirable for patients to abstain from alcohol during treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

CONCERTA should not be used in pregnancy as safety has not been established. Teratogenicity has been shown in laboratory animals.

Lactation

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. Mothers breastfeeding their infants should not be treated with CONCERTA.

4.7 Effects on ability to drive and use machines

CONCERTA 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

Clinical Trial Data

The table below shows all the adverse drug reactions (ADRs) observed during clinical trials of children, adolescents and adults with CONCERTA and those, which have been reported with other methylphenidate hydrochloride formulations. If the ADRs with CONCERTA and the methylphenidate formulation frequencies were different, the highest frequency of both databases was used.

Frequency estimate:

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)

Not known (cannot be estimated from the available data)

Table 2

System Organ Class	**Adverse Drug Reaction**
	Frequency

	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Nasopharyngitis, upper respiratory tract infection*, sinusitis *				
Blood and lymphatic system disorders					Anaemia** , Leucopenia**	
Metabolism and nutritional disorders		Anorexia, decreased appetite**, moderately reduced weight and height gain during prolonged use in children				

Psychiatric disorders	Insomnia, nervousness	Anorexia, affect lability, aggression, agitation, anxiety**, depression*, irritability, abnormal behaviour, mood swings, tics, initial insomnia*, depressed mood*, depression**, libido decreased*, tension *, bruxism*, panic attack*	Psychotic disorders, anger, suicidal ideation, mood altered, restlessness**, tearfulness, worsening of pre-existing tics of Tourette's syndrome, hypervigilance, sleep disorder	Libido disorder , confusional state**	Suicidal attempt (including completed suicide)**, transient depressed mood, abnormal thinking, apathy**, repetitive behaviours, over-focussing	Delusions**, thought disturbances, dependence, cases of abuse and dependence have been described more often with immediate release formulations
Nervous system disorders	Headache	Dizziness, psychomotor hyperactivity, somnolence, paresthaesia	Sedation, tremor**, lethargy*		Choreo-athetoid movements, reversible ischaemic neurological	Cerebrovascular disorders** (including vasculitis, cerebral

		, tension headache			deficit, neuroleptic malignant syndrome (NMS; reports were poorly documented and in most cases, patients were also receiving other medicines, so the role of methylphenidate is unclear)	haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), migraine**
Eye disorder		Accommodation disorder*	Blurred vision**, Dry eye *	Difficulties in visual accommodation		
Ear and labyrinth disorders		Vertigo*				

Cardiac disorders		Arrhythmia, tachycardia, palpitations	Chest pain		Cardiac arrest, myocardial infarction	
Vascular disorders		Hypertension	Hot flush*		Cerebral arteritis and/or occlusion, peripheral coldness**	
Respiratory, thoracic and mediastinal disorders		Cough, oropharyngeal pain	Dyspnoea**			
Gastrointestinal disorders		Abdominal pain upper, diarrhoea, nausea**, abdominal discomfort, vomiting, dry mouth **, dyspepsia*	Constipation**			
Hepatobiliary disorders			Hepatic enzyme elevations		Abnormal liver function,	

					including hepatic coma	
Skin and subcutaneous tissue disorders		Pruritis, rash, urticaria	Angioneurotic oedema, bullous conditions, exfoliative conditions	Hyperhidrosis**, Macular rash	Erythema multiforme, exfoliative dermatitis, fixed medicine eruption	
Musculoskeletal and connective tissue disorders		Muscle tightness*, muscle spasms*			Muscle cramps	
Renal and urinary disorders			Haematuria, pollakiura			
Reproductive system and breast disorders		Erectile dysfunction*		Gynaecomastia		Priapism*, Erection increased*, Prolonged erection*
General disorders and		Pyrexia, growth retardation			Sudden cardiac death	

administration site conditions		during prolonged use in children, fatigue**, irritability *, feeling jittery*, asthenia*, thirst*				
Investigations		Changes in blood pressure and heart rate (usually an increase), weight decreased, alanine aminotransferase increased *	Cardiac murmur			

*****Frequency derived from adult clinical trials and not on data from trials in children and adolescents; may also be relevant for children and adolescents.

**Frequency derived from clinical trials in children and adolescent and reported at a higher frequency in clinical trials in adult patients.

Postmarketing Data

Adverse Reactions identified during post-marketing experience with CONCERTA are included in Table 3. In Table 3, Adverse Reactions are presented by frequency category based on spontaneous reporting rates.

Table 3. Adverse Reactions Identified During Postmarketing Experience with CONCERTA

Blood and Lymphatic System Disorders
Pancytopenia, thrombocytopenia, thrombocytopenic purpura
Immune System Disorders
Hypersensitivity reactions such as angioedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, pruritus NEC, rashes, eruptions and exanthemas NEC
Psychiatric Disorders
Disorientation, hallucination, auditory hallucination, visual hallucination, mania, logorrhoea, libido disorder
Nervous System Disorders
Convulsion, grand mal convulsion, dyskinesia
Cerebrovascular disorder (including cerebral vasculitis, cerebral haemorrhage, cerebral arteritis, cerebral occlusion)
Eye Disorders
Diplopia, mydriasis, visual impairment
Cardiac Disorders

Angina pectoris, bradycardia, extrasystoles, supraventricular tachycardia, ventricular extrasystoles

Vascular Disorders

Raynaud's phenomenon

Respiratory and Thoracic and Mediastinal Disorders

Epistaxis

Hepato-biliary disorders

Hepatocellular injury

Acute hepatic failure

Skin and Subcutaneous Tissue Disorders

Alopecia, erythema

Musculoskeletal and Connective Tissue Disorders

Arthralgia, myalgia, muscle twitching

Reproductive System and Breast Disorders

Priapism

General Disorders and Administration Site Conditions

Decreased therapeutic response

chest pain, chest discomfort, decreased drug effect, hyperpyrexia

Investigations

Increased blood alkaline phosphatase, increased blood bilirubin, increased hepatic enzyme, decreased platelet count, abnormal white blood cell count

Reporting of side effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:**

https://www.sahpra.org.za/Publications/Index/8

By reporting side effects, you can help provide more information on the safety of CONCERTA.

4.9 Overdose

Signs and symptoms of CONCERTA, in overdosage, result principally from overstimulation of the CNS and excessive sympathomimetic stimulations. They may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions, coma, grand mal convulsion, euphoria, confusional state, confusion, hallucinations (auditory and/or visual), hyperhidrosis, flushing, headache, pyrexia, tachycardia, palpitations, heart rate increased, sinus dysrrhythmias, hypertension, mydriasis, and dry mouth.

Treatment consists of appropriate supportive measures. The patients must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. The efficacy of activated charcoal has not been established. Intensive

care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for pyrexia.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 1.2 Psychoanaleptics (antidepressants)

Methylphenidate HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in attention deficit hyperactivity disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of extended-release methylphenidate to adults, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 to 2 hours, then increase gradually over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours after which a gradual decrease in plasma levels of methylphenidate begins.

The mean pharmacokinetic parameters in 36 adults following the administration of extended-release methylphenidate 18 mg once daily are summarised in Table 4.

Table 4.

Mean ± SD Pharmacokinetic Parameters

PARAMETERS	**Extended-release methylphenidate (18 mg once daily) (n=36)**
C_{max} (ng/mL)	**3,7 ± 1,0**
T_{max} (h)	**6,8 ± 1,8**
AUC_{inf} (ng·h/mL)	**41,8 ± 13,9**
$t_{1/2}$ (h)	**3,5 ± 0,4**

No differences in the pharmacokinetics of extended-release methylphenidate were noted following single and repeated once daily dosing indicating no significant accumulation. The AUC and $t_{½}$ following repeated once daily dosing are similar to those following the first dose of extended-release methylphenidate.

Dose proportionality*:* Following administration of extended-release methylphenidate in single doses of 18, 36, and 54 mg/day to healthy adults, C_{max} and $AUC_{(0\text{-}inf)}$ of d-methylphenidate were proportional to dose, whereas l-methylphenidate C_{max} and $AUC_{(0\text{-}inf)}$ increased disproportionately with respect to dose. Following administration of extended-release methylphenidate, 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 extended-release methylphenidate doses from 54 to 144 mg/day resulted in linear and dose proportional increases in C_{max} and AUC_{inf} for total methylphenidate (MPH) and its major metabolite,

(alpha)-phenyl-piperidine acetic acid (PPAA). The single dose and steady state (Day 4) clearance and half-life parameters were similar, indicating that there was no time dependency in the pharmacokinetics of methylphenidate. The ratio of metabolite (PPAA) to parent drug (MPH) was constant across doses from 54 to 144 mg/day, both after single dose and upon multiple dosing.

In a multiple dose study in adolescents ADHD patients aged 13 –16 administered a dose of 18 to 72 mg/day of extended-release methylphenidate, mean C_{max} and AUC_{TAU} of methylphenidate increased proportionally with respect to the dose.

Distribution

Plasma methylphenidate concentrations in adults decline biexponentially following oral administration. The half-life of both d- and l-isomers of methylphenidate in adults following oral administration of extended-release methylphenidate was approximately 3,5 h.

Biotransformation and Elimination

In humans, methylphenidate is metabolised primarily by de-esterification to (alpha)-phenyl-piperidine acetic acid (PPAA) which has little or no pharmacologic activity.

After oral dosing of radio labelled methylphenidate in humans, about 90 % of the radioactivity was recovered in urine. The main urinary metabolite was (PPAA), accounting for approximately 80 % of the dose.

Food effects: There were no differences in either the pharmacokinetics or the pharmacodynamic performance of extended-release methylphenidate when administered after a high fat breakfast in patients. There is no evidence of dose dumping in the presence or absence of food.

Alcohol effect

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

Special populations

Gender: In healthy adults, the mean dose-adjusted $AUC_{(0\text{-}inf)}$ values for extended-release methylphenidate were 36,7 ng.h/mL in men and 37,1 ng.h/mL in women, with no difference noted between the two groups.

Age: The pharmacokinetics of extended-release methylphenidate has not been studied in children less than 6 years of age.

Renal insufficiency: There is no experience with the use of extended-release methylphenidate in patients with renal insufficiency. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of extended-release methylphenidate.

Hepatic insufficiency: There is no experience with the use of extended-release methylphenidate in patients with hepatic insufficiency.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide and triacetin.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C.

Keep out of reach of children.

6.5 Nature and contents of container

CONCERTA is available in a square, white opaque high-density polyethylene (HDPE) bottle with a white polypropylene child resistant closure, with induction sealed tamper-evident membrane. Each HDPE bottle contains one or two desiccants and will hold 30 tablets. The HDPE bottle is packed into an outer carton until required for use.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (PTY) LTD

(Reg.No. 1980/011122/07)

2 Medical Road, Halfway House,

Midrand 1685, South Africa

RA-JACZA-Medinfo@its.jnj.com

8. REGISTRATION NUMBER(S)

18 mg: 37/1.2/0322

27 mg: 42/1.2/0282

36 mg: 37/1.2/0323

54 mg: 37/1.2/0324

Namibia. Reg. No.:
18 mg: 06/1.2/0028
27 mg:10/1.2/0500
36 mg: 06/1.2/0029
54 mg: 06/1.2/0030
NS 4

Botswana Reg. No.:18/27/36/54mg:
BOT. 1302298/9/300/01
S6

Zimbabwe Reg. No.:18/27/37/54 mg
2014/13.7/4873/4/5/6
N

9. DATE OF FIRST AUTHORISATION

18 mg, 36 mg, 54 mg – 28 May 2004

27 mg – 04 Dec 2009

10. DATE OF REVISION OF THE TEXT

23 February 2024