PRODUCT NAME

CONCERTA™ (methylphenidate hydrochloride) extended-release tablets

DOSAGE FORMS AND STRENGTHS

Each extended-release tablet for once-a-day oral administration contains 18 mg, 27 mg, 36 mg, or 54 mg of methylphenidate hydrochloride.

Extended-release tablets for oral use:

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

27 mg: Capsule-shaped gray 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.

For excipients, see List of Excipients.

CLINICAL INFORMATION

Indications

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

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

Dosage and Administration

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

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

CONCERTA may be administered with or without food (see Pharmacokinetic Properties, Food Effects).

Patients New to Methylphenidate

The recommended starting dose of CONCERTA for patients, who are not currently taking methylphenidate, or stimulants other than methylphenidate, is 18 mg once daily for children and adolescents and 18 or 36 mg once daily for adults.

Patients Currently Using Methylphenidate

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

Recommended Dose Conversion from Methylphenidate Regimens to CONCERTA	
Previous Methylphenidate Daily Dose	**Recommended CONCERTA Starting Dose**
5 mg Methylphenidate twice daily or three times daily	18 mg every morning
10 mg Methylphenidate twice daily or three times daily	36 mg every morning
15 mg Methylphenidate twice daily or three times daily	54 mg every morning
20 mg Methylphenidate twice daily or three times daily	72 mg every morning

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

Dose Titration

Dosage should be individualized according to the needs and responses of the patient. Doses may be increased in 18 mg increments at weekly intervals. Daily dosages above 54 mg in children, 72 mg in adolescents, and 108 mg in adults have not been studied and are not recommended.

Maintenance/Extended Treatment

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

Dose Reduction and Discontinuation

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

Special Populations

Pediatrics (under 6 years of age)

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

Elderly (over 65 years of age)

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

Contraindications

CONCERTA is contraindicated:

- in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms;
- in patients known to be hypersensitive to methylphenidate or other components of the product;
- in patients with glaucoma;
- in patients with a family history or diagnosis of Tourette's syndrome;
- during treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a MAO inhibitor (hypertensive crises may result) (see Interactions).

Warnings and Precautions

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.

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

CNS stimulants, including methylphenidate, have been associated with the onset or exacerbation of motor and verbal tics. Therefore, clinical evaluation for tics in patients should precede use of stimulant medication. Family history should be assessed.

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

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

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

controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA should only be used in patients who are able to swallow the tablet whole.
CONCERTA should not be used to treat severe depression and/or for the prevention or treatment of normal fatigue states.
Psychotic (e.g., hallucinations) or manic symptoms have been reported in patients without a prior history of psychotic illness or mania during treatment with CONCERTA at usual doses. If such symptoms occur, consideration should be given to a possible causal role of CONCERTA and discontinuation of treatment may be appropriate (see Adverse Reactions).
Patients beginning treatment with CONCERTA should be monitored for the appearance or worsening of aggressive behavior. Aggression is frequently associated with ADHD; however, emergence or worsening of aggression has been reported during treatment with CONCERTA (see Adverse Reactions).
CONCERTA should be given with caution in the following conditions:

- Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.
- In the laboratory classroom clinical trials in children, both CONCERTA and methylphenidate three times daily increased resting pulse by an average of 2 to 6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1 to 4 mm Hg during the day, relative to placebo. In placebo-controlled studies in adults, mean increases in resting pulse rate of approximately 4 to 6 bpm were observed with CONCERTA at endpoint vs. a mean change of roughly –2 to 3 bpm with placebo. Mean changes in blood pressure at endpoint ranged from about –1 to 1 mm Hg (systolic) and 0 to 1 mm Hg (diastolic) for CONCERTA and from -1 to 1 mm Hg (systolic) and –2 to 0 mm Hg (diastolic) for placebo. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate.
- CONCERTA should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.
- 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.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.
Periodic hematologic monitoring (Complete Blood Count, differential, and platelet counts) is advised during prolonged therapy.

Interactions

CONCERTA should not be used in patients being treated (currently or within the preceding 2 weeks) with MAO inhibitors (see Contraindications)
Because of possible increases in blood pressure, CONCERTA should be used cautiously with vasopressor agents.
Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some

antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

Pregnancy, Breast-feeding and Fertility

Pregnancy

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

Methylphenidate hydrochloride has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times the maximum recommended human dose on a mg/kg basis.

Teratogenic effects were not seen in rats at methylphenidate hydrochloride doses up to 30 mg/kg/day, resulting in an approximate systemic exposure to methylphenidate of nine to twelve times that seen in trials in volunteers and patients with the maximum recommended dose of CONCERTA, based on pharmacokinetic data.

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

Breast-feeding

It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if CONCERTA is administered to a nursing woman.

Effects on Ability to Drive and Use Machines

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

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of methylphenidate 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 the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Data

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

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

Pediatric Patients

The safety of CONCERTA was evaluated in 639 pediatric (children and adolescents) subjects 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 in these trials are shown in Table 1.

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

System/Organ Class Adverse Drug Reaction	CONCERTA (n=321) %	Placebo (n=318) %
Infections and Infestations		
Nasopharyngitis	2.8	2.2
Psychiatric Disorders		
Insomnia*	2.8	0.3
Nervous System Disorders		
Dizziness	1.9	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1.9	0.9
Oropharyngeal pain	1.2	0.9
Gastrointestinal Disorders		
Abdominal pain upper	6.2	3.8
Vomiting	2.8	1.6
General Disorders and Administration Site Conditions		
Pyrexia	2.2	0.9

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

The majority of 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 reported by ≥ 1% of CONCERTA-treated adult subjects in these trials are shown in Table 2

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

System/Organ Class Adverse Drug Reaction	CONCERTA (n=596) %	Placebo (n=309) %
Infections and Infestations		
Upper respiratory tract infection	1.7	1.0
Sinusitis	1.3	1.0
Metabolism and Nutrition Disorders		
Decreased appetite	24.8	6.1
Anorexia	4.2	1.3
Psychiatric Disorders		
Insomnia	13.3	7.8
Anxiety	8.4	2.9
Initial insomnia	5.7	2.6
Depressed mood	4.4	2.6
Restlessness	4.0	0
Agitation	3.2	0.6
Nervousness	2.3	0.6
Bruxism	1.5	0.6
Depression	1.5	0.6
Affect lability	1.3	0.6

Libido decreased	1.3	0.6
Panic attack	1.3	0.3
Tension	1.3	0.3
Aggression	1.2	0.6
Confusional state	1.0	0.3
Nervous System Disorders		
Headache	24.2	18.8
Dizziness	7.4	5.5
Tremor	3.4	0.6
Paresthesia	1.2	0
Tension headache	1.0	0.3
Eye Disorders		
Accommodation disorder	1.3	0
Vision blurred	1.3	1.0
Ear and Labyrinth Disorders		
Vertigo	2.0	0.3
Cardiac Disorders		
Tachycardia	6.0	0
Palpitations	4.5	0.6
Vascular Disorders		
Hypertension	2.2	1.6
Hot flush	1.3	0.6
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal pain	1.5	1.3
Cough	1.2	1.0
Dyspnea	1.2	0.6
Gastrointestinal Disorders		
Dry mouth	15.1	3.6
Nausea	14.3	4.9
Dyspepsia	2.0	1.9
Vomiting	1.8	0.6
Constipation	1.5	0.6
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	5.7	1.3
Musculoskeletal and Connective Tissue Disorders		
Muscle tightness	1.3	0
Muscle spasms	1.0	0.3
Reproductive System and Breast Disorders		
Erectile dysfunction	1.0	0.3
General Disorders and Administration Site Conditions		
Irritability	5.2	2.9
Fatigue	4.7	4.2
Thirst	1.8	0.6
Asthenia	1.2	0
Investigations		
Weight decreased	8.7	3.6
Heart rate increased	3.0	1.9
Blood pressure increased	2.5	1.9

Alanine aminotransferase increased	1.0	0

The 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 pediatric 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 reported by ≥ 1% of CONCERTA-treated subjects in these trials and not listed in Tables 1 and 2 are shown in Table 3.

Table 3. Adverse Drug Reactions Reported by ≥ 1% of CONCERTA-Treated Subjects in 12 Open-Label Clinical Trials

System/Organ Class Adverse Drug Reaction	**CONCERTA (n=3782) %**
Psychiatric Disorders	
Tic	2.0
Mood swings	1.1
Nervous System Disorders	
Somnolence	1.0
Gastrointestinal Disorders	
Diarrhea	2.4
Abdominal discomfort	1.3
Abdominal pain	1.2
Skin and Subcutaneous Tissue Disorders	
Rash	1.3
General Disorders and Administration Site Conditions	
Feeling jittery	1.4

The majority of 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 pediatric and adult subjects in the double-blind and open-label clinical datasets are listed in Table 4.

Table 4. Adverse Drug Reactions Reported by < 1% of CONCERTA-Treated Pediatric and Adult Subjects in Either Double-Blind or Open-Label Clinical Trials

System/Organ Class Adverse Drug Reaction
Blood and Lymphatic System Disorders
Leucopenia
Psychiatric Disorders
Anger, Sleep disorder, Hypervigilance, Tearfulness, Mood altered
Nervous System Disorders
Psychomotor hyperactivity, Sedation, Lethargy
Eye Disorder
Dry eye
Skin and Subcutaneous Tissue Disorders
Rash macular
Investigations
Cardiac murmur

The majority of ADRs were mild to moderate in severity.

Postmarketing Data

ADRs identified during postmarketing experience with CONCERTA are included in Tables 5. The frequencies are provided according to the following convention:

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

In Table 5, ADRs are presented by frequency category based on spontaneous reporting rates.

Table 5. Adverse Drug Reactions Identified During Postmarketing Experience with CONCERTA by Frequency Category Estimated from Spontaneous Reporting Rates

Blood and Lymphatic System Disorders	
Very rare	Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura
Immune System Disorders	
Rare	Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions and Exanthemas NEC
Psychiatric Disorders	
Very rare	Disorientation, Hallucination, Hallucination auditory Hallucination, visual, Mania, Logorrhea
Nervous System Disorders	
Very rare	Convulsion, Grand mal convulsion, Dyskinesia
Eye Disorders	
Very rare	Diplopia, Mydriasis, Visual impairment
Cardiac Disorders	
Very rare	Angina pectoris, Bradycardia, Extrasystoles, Supraventricular tachycardia, Ventricular extrasystoles
Vascular Disorders	
Very rare	Raynaud's phenomenon
Skin and Subcutaneous Tissue Disorders	
Very rare	Alopecia, Erythema
Musculoskeletal and Connective Tissue Disorders	
Very rare	Arthralgia, Myalgia, Muscle twitching
General Disorders and Administration Site Conditions	
Rare	Therapeutic response decreased
Very rare	Chest pain, Chest discomfort, Drug effect decreased, Hyperpyrexia
Investigations	
Very rare	Blood alkaline phosphatase increased, Blood bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal

Overdose

Symptoms and signs

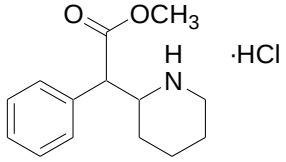
Signs and symptoms of CONCERTA overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, muscle twitching, convulsion, grand mal convulsion, confusional state, hallucination (auditory and/or visual), hyperhidrosis,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

Treatment

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present.

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 hemodialysis for CONCERTA overdosage has not been established. The prolonged release of methylphenidate from CONCERTA should be considered when treating patients with overdose.

PHARMACOLOGICAL PROPERTIES



Pharmacodynamic Properties

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

Mechanism of action

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

Pharmacokinetic Properties

Absorption

Methylphenidate is readily absorbed. Following oral administration of CONCERTA to adults, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 to 2 hours, then increase gradually over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours after which a gradual decrease in plasma levels of methylphenidate begins. CONCERTA once daily minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily. The relative bioavailability of CONCERTA once daily and methylphenidate three times daily in adults is comparable.
The mean pharmacokinetic parameters in 36 adults following the administration of CONCERTA 18 mg once daily and methylphenidate hydrochloride 5 mg three times daily are summarized in Table 6.

Table 6
Mean ± SD Pharmacokinetic Parameters

Parameters	CONCERTA (18 mg once daily) (n=36)	Methylphenidate hydrochloride (5 mg three times daily) (n=35)
C_{max} (ng/ml)	3.7 ± 1.0	4.2 ± 1.0
T_{max} (h)	6.8 ± 1.8	6.5 ± 1.8
AUC_{inf} (ng h/ml)	41.8 ± 13.9	38.0 ± 11.0
$t_{1/2}$ (h)	3.5 ± 0.4	3.0 ± 0.5

No differences in the pharmacokinetics of CONCERTA were noted following single and repeated once daily dosing indicating no significant drug accumulation. The AUC and $t_{½}$

following repeated once daily dosing are similar to those following the first dose of CONCERTA.

Dose Proportionality

Following administration of CONCERTA in single doses of 18, 36, and 54 mg/day to healthy adults, C max and AUC(0-inf) of d-methylphenidate were proportional to dose, whereas l-methylphenidate Cmax and AUC(0-inf) increased disproportionately with respect to dose. Following administration of CONCERTA, plasma concentrations of the l-isomer were approximately 1/40th the plasma concentrations of the d-isomer.

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

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

Distribution

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

Metabolism

In humans, methylphenidate is metabolized primarily by de-esterification to PPAA which has little or no pharmacologic activity. In adults, the metabolism of CONCERTA once daily as evaluated by metabolism to PPAA is similar to that of methylphenidate three times daily. The metabolism of single and repeated once daily doses of CONCERTA is similar.

Elimination

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

Food Effects

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

Special Populations

Gender

In healthy adults, the mean dose-adjusted AUC(0-inf) values for CONCERTA were 36.7 ng h/ml in men and 37.1 ng h/ml in women, with no differences noted between the two groups.

Race

In adults receiving CONCERTA, dose-adjusted AUC(0-inf) was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age

The pharmacokinetics of CONCERTA has not been studied in children less than 6 years of age.

Renal Insufficiency

There is no experience with the use of CONCERTA in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively

metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPAA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of CONCERTA.

Hepatic Insufficiency

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

NON-CLINICAL INFORMATION

In a lifetime carcinogenicity study carried out in mice, methylphenidate hydrochloride caused an increase in hepatocellular adenomas, and in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This is considerably higher than the recommended human dose on a mg/kg basis. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

A similar lifetime study in the rat at a methylphenidate hydrochloride dose of up to 45 mg/kg/day showed no evidence of carcinogenicity. In a 24-week study in the transgenic mouse strain p53+/-, there was no evidence of carcinogenicity at methylphenidate hydrochloride doses of up to 74 mg/kg/day.

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

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

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

PHARMACEUTICAL INFORMATION

List of Excipients

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

Incompatibilities

Not known.

Shelf Life

See expiry date on the outer pack.

Storage Conditions

Store at 25°C. Keep the container tightly closed.

Keep out of the reach of children.

Nature and Contents of Container

CONCERTA is available in high-density polyethylene (HDPE) bottles. Each HDPE bottle contains either 30 or 100 tablets, and desiccant.

Instructions for Use and Handling

No special requirements.

Instructions for Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

MANUFACTURED BY
See outer carton.

DATE OF REVISION OF THE TEXT
15 May 2012