PRODUCT NAME
CONCERTA® (methylphenidate hydrochloride)

DOSAGE FORMS AND STRENGTHS
Extended-release tablets:

18 mg tablet
Capsule-shaped yellow tablet with "alza 18" printed on one side in black ink. Each tablet contains 18 mg of methylphenidate hydrochloride.

27 mg tablet
Capsule-shaped gray tablet with "alza 27" printed on one side in black ink. Each tablet contains 27 mg of methylphenidate hydrochloride.

36 mg tablet
Capsule-shaped white tablet with "alza 36" printed on one side in black ink. Each tablet contains 36 mg of methylphenidate hydrochloride.

54 mg tablet
Capsule-shaped brownish-red tablet with "alza 54" printed on one side in black ink. Each tablet contains 54 mg of methylphenidate hydrochloride.

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.

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. The symptoms must cause clinically significant impairment, eg, in social, academic, or occupational functioning, and be present in two or more settings, eg, school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive type, at least six of the following symptoms must have persisted for at least 6 months, lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months; fidgeting/squirming; leaving seat; inappropriate running/climbing; difficult with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations
Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate

diagnosis requires the use of medical and special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the purpose of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

CONCERTA® is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child 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 child's symptoms.

Long-Term Use

The effectiveness of CONCERTA® for long-term use, ie, for more than 4 weeks, 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 (see *Dosage and Administration*).

Dosage and Administration

Dosage

Patients new to methylphenidate

The recommended starting dosage 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 to 36 mg once daily for adults.

Patients currently using methylphenidate

The recommended dosage of CONCERTA® for patients who are currently taking methylphenidate twice daily or three times daily at dosages of 10 to 60 mg/day is provided in Table 1.

Table 1. Recommended Dosage Conversion from Methylphenidate Regimens to CONCERTA®

Previous Methylphenidate Daily Dose	Recommended CONCERTA® Starting Dosage
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 starting dose for patients currently taking methylphenidate in other regimens.

Dose titration

The 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 have not been studied and are not recommended. Daily dosages above 72 mg in adults are not recommended.

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

Maintenance/extended treatment

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

Nevertheless, 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. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose reduction and discontinuation

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

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

Administration

CONCERTA® 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 *Precautions – Information for Patients*).
CONCERTA® may be administered with or without food (see *Pharmacokinetic Properties – Food effects*).

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.

Long-term effects of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (ie 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.

Elderly (over 65 years of age)

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

Renal insufficiency
There is no experience with the use of CONCERTA® in patients with renal insufficiency (see *Pharmacokinetic Properties – Special populations, Renal insufficiency*).

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

Contraindications
CONCERTA® is contraindicated:

- in patients known to be hypersensitive to methylphenidate or other components of the product;
- in patients with glaucoma;
- during treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase (MAO) inhibitor (hypertensive crisis may result) (see *Interactions*);
- in patients with hyperthyroidism;
- in patients with severe angina pectoris;
- in patients with cardiac arrhythmia;
- in patients with phaeochromocytoma.

Warnings
Motor and verbal tics, and worsening of Tourette's syndrome
Central nervous system (CNS) stimulants, including methylphenidate, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. It is recommended that the family history be assessed, and that the patient is clinically evaluated for tics or Tourette's syndrome before initiating methylphenidate. Regular monitoring for the emergence or worsening of tics or Tourette's syndrome during treatment with methylphenidate is recommended at every dose adjustment and every visit, and treatment discontinued if clinically appropriate.

Depression
CONCERTA® should not be used to treat severe depression.

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

Long-Term Suppression of Growth
Sufficient data on the safety of long-term use of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (ie, 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.

Psychosis
Clinical experience suggests that in psychotic patients, administration of methylphenidate may

exacerbate symptoms of behavior disturbance and thought disorder.

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients.

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 Behaviour and Ideation

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

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

Seizures

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

Potential for Gastrointestinal Obstruction

Because the CONCERTA® tablet is non-deformable and does not appreciably change in shape in the GI tract, CONCERTA® should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: small bowel inflammatory disease, “short gut” syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudo-obstruction, or Meckel’s diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in 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 (see *Precautions - Information for Patients*).

Hypertension and other Cardiovascular Conditions

Use cautiously in patients with hypertension. Cardiovascular status and blood pressure should be monitored at appropriate intervals in patients taking CONCERTA®, especially patients with

hypertension. In the laboratory classroom clinical trials in children (Studies 1 and 2), both CONCERTA® and methylphenidate tid increased resting pulse by an average of 2 to 6 bpm and produced average increases of systolic and diastolic blood pressure of roughly1 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 increase in blood pressure or heart rate, eg. those with preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism.

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

Increased intraocular pressure and glaucoma

There have been reports of a transient elevation of intraocular pressure (IOP) associated with methylphenidate treatment. The use of CONCERTA® in patients with glaucoma is contraindicated (*See Contraindications*). Patients at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) must be closely monitored.

Serious Cardiovascular Events

Children and Adolescents

Sudden death has been reported in association with central nervous system (CNS) stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults

Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

It is essential that children, adolescents or adults with pre-existing structural cardiac abnormalities or other serious heart problems being considered for treatment are assessed by a

cardiologist before initiating treatment. Ongoing cardiologist supervision should be maintained throughout treatment in these patients.

Aggression, anxiety and agitation

Aggressive behavior, marked anxiety, or agitation are often observed in patients with ADHD, and have been reported in patients treated with CONCERTA® (see Adverse Reactions). Anxiety led to discontinuation of CONCERTA® in some patients. It is recommended to monitor patients beginning treatment with CONCERTA® for the appearance of, or worsening of, aggressive behavior, marked anxiety, or agitation.

Priapism

Prolonged and painful erections requiring immediate medical attention (sometimes including surgical intervention), have been reported with methylphenidate products, including CONCERTA®, in both pediatric and adult patients (see *Adverse Reactions*). 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 Adverse Reactions). 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.

Drug Dependence

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. 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.

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.

Precautions

Hematologic Monitoring

Periodic hematologic monitoring (Complete Blood Count, differential, and platelet counts) is advised during prolonged therapy.

Information for patients

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a lifetime carcinogenicity study carried out in B8C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause increases in tumors in a lifetime carcinogenicity study carried out in F344 rats, the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the life-time carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the in vitro Ames reverse mutation assay or the in vitro mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an in vitro assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative in vivo in males and females in the mouse bone marrow micronucleus assay.

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of CONCERTA® on a mg/kg and mg/m basis, respectively.

Pregnancy: Teratogenic Effects

Pregnancy Category C: Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the

maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30/mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPAA in pregnant rats was 2 times that seen in trials in volunteers and patients with the maximum recommended dose of CONCERTA® based on the AUC.

The safety of methylphenidate for use during human pregnancy has not been established. There are no adequate and well controlled studies in pregnant women, CONCERTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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 nursing woman.

Pediatric Use

The safety and efficacy of CONCERTA® in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (see *Special Populations*).

Effects on Ability to Drive and Use Machines

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

Interactions

CONCERTA® should not be used in patients being treated (currently or within the preceding two weeks) with MAO inhibitors (see *Contraindications*).

Because of possible effects on blood pressure, CONCERTA® should be used cautiously with vasopressor agents.

CONCERTA® 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 *Warnings – Hypertension and other Cardiovascular Conditions*).

Concomitant use of halogenated anesthetics 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 anesthetics on the day of surgery.

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.

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.

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.

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 hydrochloride based on the comprehensive assessment of the available adverse event information. A causal relationship with methylphenidate hydrochloride usually 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 reactions reported at ≥1% frequency

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

Pediatric Patients

The safety of CONCERTA® was evaluated in 639 pediatric patients (children and adolescents) with ADHD who participated in 4 placebo-controlled, double-blind clinical trials. Three of the studies were conducted in children aged 6-12 years of age: two were cross-over studies in which patients received CONCERTA® (doses of either 18 mg, 36 mg or 54 mg per day), immediate release methylphenidate and placebo for each of 7 days. The third study was a parallel group comparison in which patients were randomised to CONCERTA® (doses of either 18 mg, 36 mg or 54 mg per day), immediate release methylphenidate or placebo for 28 days. In a fourth study, adolescents aged 13-18 years, receiving CONCERTA® doses of 18 mg, 36 mg, 54 mg or 72 mg per day were randomised into a two week placebo-controlled, double-blind phase following an open-label 4 weeks titration phase. The information presented in this section was derived from pooled data.

Adverse reactions reported by ≥1% of CONCERTA®-treated children and adolescent patients in these trials are shown in Table 2.

Table 2. Adverse Reactions Reported by ≥1% of CONCERTA®-Treated Children and Adolescent Patients in 4 Placebo-Controlled, Double-Blind Clinical Trials

System/Organ Class Adverse 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		
Headache	10.6	11.9
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 adverse reactions were mild to moderate in severity.

Adult Patients

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

Adverse reactions reported by ≥1% of CONCERTA®-treated adult patients in these trials are shown in Table 3.

Table 3. Adverse Reactions Reported by ≥1% of CONCERTA®-Treated Adult Patients in 3 Placebo-Controlled, Double-Blind Clinical Trials		
System/Organ Class Adverse 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	0
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*	1.5	0.6
Panic attack	1.3	0.3
Tension	1.3	0.3
Aggression	1.2	0.6
Confusional state	1.0	0.3
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

Table 3. Adverse Reactions Reported by ≥1% of CONCERTA®-Treated Adult Patients in 3 Placebo-Controlled, Double-Blind Clinical Trials		
System/Organ Class Adverse Reaction	**CONCERTA®** **(n=596)** %	**Placebo** **(n=309)** %
Musculoskeletal and Connective Tissue Disorders		
Muscle tightness	1.3	0
Muscle spasms	1.0	0.3
Reproductive System and Breast Disorder		
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 adverse reaction Libido decreased includes the preferred term Loss of libido

The majority of adverse reactions were mild to moderate in severity.

Open-label data – Adverse reactions reported at ≥1% frequency

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

Adverse reactions reported by ≥1% of CONCERTA®-treated patients in these trials and not listed in Tables 2 and 3 are shown in Table 4.

Table 4. Adverse Reactions Reported by ≥1% of CONCERTA®-Treated Patients in 12 Open-Label Clinical Trials	
System/Organ Class Adverse 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 adverse reactions were mild to moderate in severity.

Double-blind and open-label data – Adverse reactions reported at <1% frequency

Additional adverse reactions that occurred in <1% of CONCERTA®-treated pediatric and adult patients in the double-blind and open-label clinical datasets are listed in Table 5.

Table 5. Adverse Reactions Reported by <1% of CONCERTA®-Treated Pediatric and Adult Patients in Either Double-Blind or Open-Label Clinical Trials
System/Organ Class
Adverse Reaction
Blood and Lymphatic System Disorders
Leukopenia
Psychiatric Disorders
Anger, Sleep disorder, Hypervigilance, Tearfulness, Mood Altered,
Nervous System Disorders
Psychomotor hyperactivity, Sedation, Lethargy,
Eye Disorders
Dry eye
Skin and Subcutaneous Tissue Disorders
Rash macular
Investigations
Cardiac murmur

The majority of adverse reactions were mild to moderate in severity.

Postmarketing data

Adverse reactions identified during postmarketing experience with CONCERTA® are included in Table 6. In this table, the frequencies are provided according to the following convention:

Very common	≥1/10 (≥10%)
Common	≥1/100 and <1/10 (≥1% and <10%)
Uncommon	≥1/1000 and <1/100 (≥0.1% and <1%)
Rare	≥1/10000 and <1/1,000 (≥0.01 and <0.1%)
Very rare	<1/10000 (<0.01%), including isolated reports
Not known	Cannot be estimated from the available data.

Table 6. Adverse Reactions Identified During Postmarketing Experience with CONCERTA®	
System Organ Class Adverse Reaction	**Frequency Category Estimated from Clinical Trials with CONCERTA®**
Blood and Lymphatic System Disorders	
Pancytopenia	Not known
Thrombocytopenia	Not known
Thrombocytopenic purpura	Not known
Immune System Disorders	
Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions and Exanthemas NEC	Uncommon
Psychiatric Disorders	
Disorientation	Rare

Hallucination	Not known
Hallucination auditory	Rare
Hallucination visual	Not known
Mania	Uncommon
Logorrhea	Uncommon
Libido disorder*	Not known
Nervous System Disorders	
Convulsion	Not known
Grand mal convulsion	Not known
Cerebrovascular disorder (including cerebral vasculitis, cerebral hemorrhage, cerebral arteritis, cerebral vascular occlusion)	Not known
Dyskinesia	Uncommon
Eye Disorders	
Diplopia	Rare
Mydriasis	Rare
Visual impairment	Rare
Cardiac Disorders	
Angina pectoris	Rare
Bradycardia	Not known
Extrasystoles	Rare
Supraventricular tachycardia	Not known
Ventricular extrasystoles	Rare
Vascular Disorders	
Raynaud's phenomenon	Not known
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Rare
Hepatobiliary Disorders	
Blood alkaline phosphatase increased	Not known
Blood bilirubin increased	Uncommon
Hepatic enzyme increased	Uncommon
Hepatocellular injury	Not known
Acute hepatic failure	Not known
Skin and Subcutaneous Tissue Disorders	
Alopecia	Uncommon
Erythema	Rare
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	Common
Myalgia	Common
Muscle twitching	Uncommon
Reproductive System and Breast Disorders	
Priapism	Not known
General Disorders and Administration Site Conditions	
Therapeutic response decreased	Not known
Chest pain	Uncommon
Chest discomfort	Uncommon
Drug effect decreased	Uncommon
Hyperpyrexia	Not known
Investigations	
Platelet count decreased	Not known
White blood cell count abnormal	Not known

NEC Not elsewhere classified

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

Suicidal Behaviour and Ideation

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

Drug Abuse and Dependence

Controlled Substance Class

CONCERTA®, like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

Abuse, Dependence, and Tolerance

See *Warnings – Drug Dependence* for warning containing drug abuse and dependence information.

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

Additional signs and symptoms of methylphenidate overdosage may include tremors, hypperreflexia, euphoria and delirium.

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 hemodialysis for CONCERTA® overdosage has not been established.

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

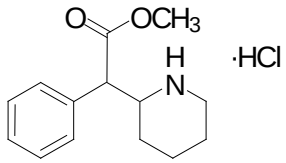
Poison Control Center

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center, for up-to-date information on the management of overdosage with methylphenidate.

Pharmacological Properties

Description

Chemically, methylphenidate hydrochloride is d,l(racemic) methylα-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is $C_{14}H_{19}NO_2 \bullet HCI$. Its structural formula is:



Methylphenidate hydrochloride USP is a white, odorless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

System Components and Performance

CONCERTA® uses osmotic pressure to deliver methylphenidate hydrochloride at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within one hour, providing an initial dose of methylphenidate. Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The membrane controls the rate at which water enters the tablet core, which in turn controls drug delivery. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell along with insoluble core components.

Pharmacodynamic Properties

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

Mechanism of action

Methylphenidate hydrochloride is a 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.

Clinical studies

CONCERTA® was demonstrated to be effective in the treatment of ADHD in 4 randomized, double-blind, placebo-controlled studies in children and adolescents and 2 double-blind placebo-controlled studies in adults who met the Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD.

Children

The controlled studies compared CONCERTA® given qd (18, 36, or 54 mg) over 12 hours (15, 30, or 45 mg total daily dose), and placebo in two single-center, 3-week crossover studies (Studies 1 and 2) and in a multicenter, 4-week, parallel-group comparison (Study 3). The primary comparison of interest in all three trials was CONCERTA® versus placebo.

Symptoms of ADHD were evaluated by community schoolteachers using the Inattention/Overactivity with Aggression (IOWA) Conners scale. Statistically significant reduction in the Inattention/Overactivity subscale versus placebo was shown consistently across all three controlled studies for CONCERTA® qd. The scores for CONCERTA® and placebo for the three studies are presented in Figure 1.

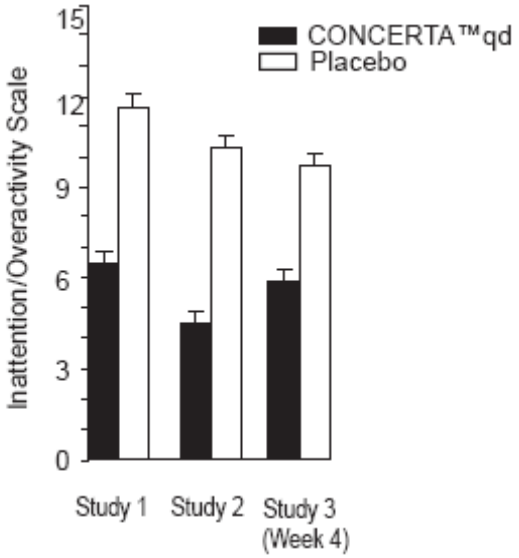
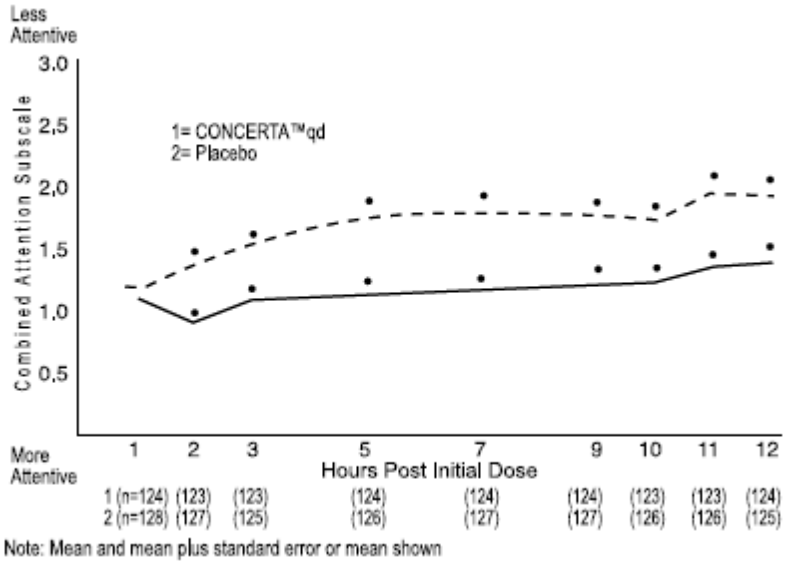


Figure 1. Mean Community School Teacher IOWA Conners Inattention/Overactivity Scores with CONCERTA® qd (18,36, or 54mg) and placebo. Studies 1 and 2 involved a 3-way crossover of 1 week per treatment arm. Study 3 involved 4 weeks of parallel group treatments with a Last Observation Carried Forward analysis at week 4. Error bars represent the mean plus standard error of the mean.

In two controlled studies (Studies 1 and 2), symptoms of ADHD were evaluated by laboratory school teachers using the SKAMP* laboratory school rating scale. The combined results from these two studies demonstrated significant improvements in attention and behavior in patients treated with CONCERTA® versus placebo that were maintained through 12 hours after dosing. Figure 2 presents the laboratory school teacher SKAMP ratings for CONCERTA® and placebo.

*Swanson, Koikin, Agler, M-Fynn and Pelham

Figure 2. Laboratory School Teacher SKAMP Ratings
Mean (SEM) of Combined Attention (Studies 1 and 2)



Note: Mean and mean plus standard error or mean shown

Adolescents

In a randomized, double blind, multi-center, placebo-controlled trial (Study 4) involving 177 patients, CONCERTA® was demonstrated to be effective in the treatment of ADHD in adolescents aged 13 to 18 and weighing 34.1 – 128.9 kg (mean [SD] = 66.0 [17.1] kg) at doses up to 72 mg/day (1.4mg/kg/day). Of 220 patients who entered an open 4-week titration phase, 177 were titrated to an individualized dose (maximum of 72 mg/day) based on meeting specific improvement criteria on the ADHD Rating Scale and the Global Assessment of Effectiveness with acceptable tolerability. Patients who met these criteria were then randomized to receive either their individualized dose of CONCERTA® (18 – 72 mg/day, n=87) or placebo (n=90) during a two-week double-blind phase. At the end of this phase, mean scores for the investigator rating on the ADHD Rating Scale demonstrated that CONCERTA® was significantly superior to placebo.

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 multicenter, parallel group, 7-week dose-titration study (Study 5) (36 to 108 mg/day) and in a multicenter, parallel group 5-week, fixed-dose study (Study 6) (18, 36, and 72 mg/day).

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 statistically significantly

superior to placebo.

Study 6 was a multicenter, 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 statistically significantly more effective than placebo in improving the CAARS (Conners' Adult ADHD Rating Scale) total scores at double blind end point in adult patients with ADHD.

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® qd minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate tid – see mean plasma concentration versus time profiles in Figure 3. The relative bioavailability of CONCERTA® qd and methylphenidate tid in adult is comparable.

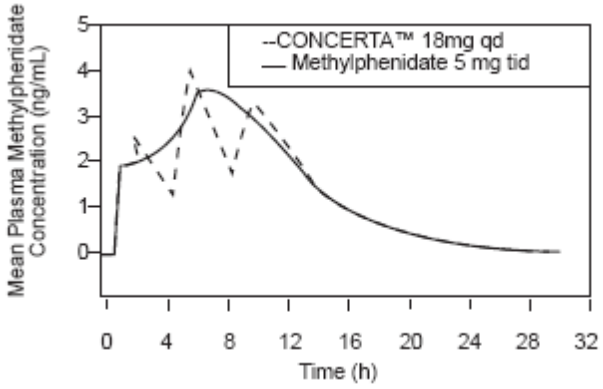


Figure 3. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of CONCERTA® 18mg qd and immediate-release methylphenidate 5 mg tid administered every 4 hours.

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 7.

Table 7. 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 qd dosing indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated qd dosing are similar to those following the first dose of CONCERTA®.

Dose proportionality

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

In 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 during a dosing interval of the d-isomer 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 3.5h.

Metabolism

In humans, methylphenidate is metabolized primarily by de-esterification to alpha phenyl piperidine acetic acid (PPAA), which has little or no pharmacologic activity. In adults the metabolism of CONCERTA® qd as evaluated by metabolism to PPAA is similar to that of methylphenidate tid. The metabolism of single and repeated qd 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_{inf} values for CONCERTA® were 36.7ng•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_{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.

PHARMACEUTICAL INFORMATION
List of Excipients
Butylated hydroxytoluene
Carnauba wax
Cellulose acetate
Hypromellose
Isopropyl alcohol
Lactose
Phosphoric acid
Poloxamer
Polyethylene glycol
Polyethylene oxides
Povidone
Propylene glycol
Sodium chloride
Stearic acid
Succinic acid
Synthetic iron oxides

Titanium dioxide
Triacetin

Incompatibilities
Not known.

Shelf Life
Refer to outer carton.

Storage Conditions
Store at 25ºC (77ºF); excursions permitted to 15-30ºC (59-88ºF) [see USP controlled Room Temperature]. Keep the container tightly closed.

Keep out of reach of children.

Nature and Contents of Container
All four dosage strengths are supplied in HDPE bottles containing 30 tablets.
- 18mg 30 count bottle
- 27mg 30 count bottle
- 36mg 30 count bottle
- 54mg 30 count bottle

Instructions for Use and Handling
No special requirements.

PRODUCT REGISTRANT
Johnson & Johnson International (Singapore) Pte. Ltd.
2 Science Park Drive
#07-13, Ascent
Singapore Science Park 1
Singapore 118222

BATCH RELEASERS
ALZA Corporation,
700 Eubanks Drive, Vacaville,
CA 95688-9470, United States

Janssen Ortho, L.L.C.
State Road 933 Km 0.1, Mamey Ward
Gurabo, Puerto Rico 00778, USA

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