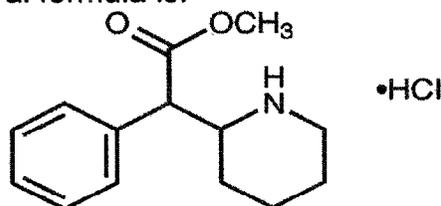


ATTACHMENT 2

Methylphenidate Hydrochloride Extended-Release Tablets (methylphenidate HCL) CII

DESCRIPTION

Methylphenidate Hydrochloride Extended-Release Tablets are a central nervous system (CNS) stimulant. Methylphenidate Hydrochloride Extended-Release Tablets are available in one tablet strength for once-a-day oral administration and contain 72 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. Chemically, methylphenidate HCl is d,l (racemic) methyl (alpha)-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is C₁₄H₁₉NO₂ ·HCl. Its structural formula is:



Methylphenidate HCl 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.

The inactive ingredients contained in Methylphenidate Hydrochloride Extended-Release Tablets will be furnished when the ANDA is submitted, since this is proprietary information. The inactive ingredients are GRAS ingredients at the appropriate levels.

System Components and Performance

Methylphenidate Hydrochloride Extended-Release Tablets are formulated to deliver methylphenidate HCl at a controlled rate and are designed to have a 12-hour duration of effect. 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. It is possible that Methylphenidate Hydrochloride Extended-Release Tablets may be visible on abdominal x-rays under certain circumstances, especially when digital enhancing techniques are utilized.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Methylphenidate Hydrochloride 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.

Pharmacokinetics

Absorption

Methylphenidate is readily absorbed. Following oral administration of Methylphenidate Hydrochloride Extended-Release Tablets, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins. Mean times to reach peak plasma concentrations across all doses of Methylphenidate Hydrochloride Extended-Release Tablets occurred between 6 to 10 hours.

Methylphenidate Hydrochloride Extended-Release Tablets qd minimize the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate tid (see Figure 1). The relative bioavailability of Methylphenidate Hydrochloride Extended-Release Tablets qd and methylphenidate tid in adults is comparable.

FIGURE 1

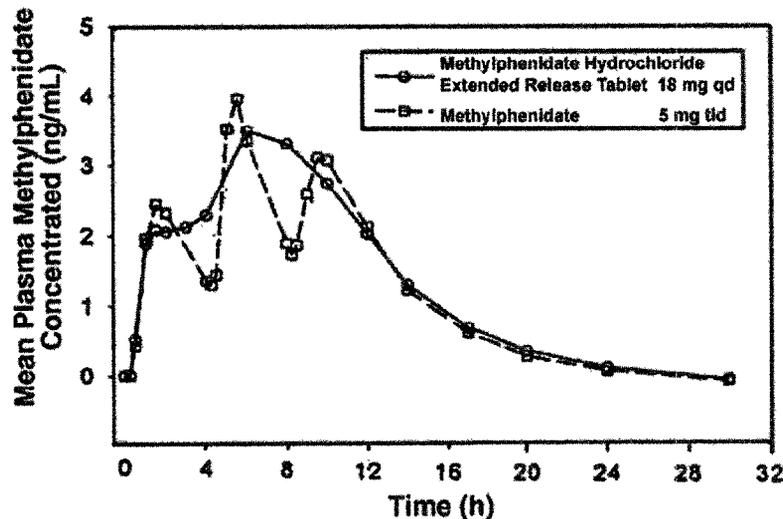


Figure 1. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of Methylphenidate Hydrochloride Extended-Release Tablets 18 mg qd and immediate-release methylphenidate 5 mg tid administered every 4 hours.

The mean pharmacokinetic parameters in 36 adults following the administration of Methylphenidate Hydrochloride Extended-Release Tablets 18 mg qd and methylphenidate 5 mg tid are summarized in Table 1.



TABLE 1
Mean ± SD Pharmacokinetic Parameters

Parameters	Methylphenidate Hydrochloride Extended Release Tablet (18 mg qd) (n=36)	Methylphenidate (5 mg tid) (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 Methylphenidate Hydrochloride Extended-Release Tablets were noted following single and repeated once-daily dosing indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated once-daily dosing are similar to those following the first dose of Methylphenidate Hydrochloride Extended-Release Tablets 18 mg.

Dose Proportionality

Following administration of Methylphenidate Hydrochloride Extended-Release Tablets in a single dose of 18, 36, and 54 mg/day to adults, C_{max} and $AUC_{(0-inf)}$ of d-methylphenidate were proportional to dose, whereas l-methylphenidate C_{max} and $AUC_{(0-inf)}$ increased disproportionately with respect to dose. Following administration of Methylphenidate Hydrochloride Extended-Release Tablets plasma concentrations of the l-isomer were approximately 1/40th the plasma concentrations of the d-isomer.

In a multiple-dose study in adolescent ADHD patients aged 13 to 16 administered their prescribed dose (18 to 72 mg/day) of Methylphenidate Hydrochloride Extended-Release Tablets, 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 Methylphenidate Hydrochloride Extended-Release Tablets was approximately 3.5 h.

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily by de-esterification to (alpha)-phenyl-piperidine acetic acid (PPA) which has little or no pharmacologic activity. In adults the metabolism of Methylphenidate Hydrochloride Extended Release Tablets qd as evaluated by metabolism to PPA is similar to that of methylphenidate tid. The metabolism of single and repeated qd doses of Methylphenidate Hydrochloride Extended Release Tablets is similar.



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

Food Effects

In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of Methylphenidate Hydrochloride Extended Release Tablets 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 Methylphenidate Hydrochloride Extended Release Tablets 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 Methylphenidate Hydrochloride Extended Release Tablets, 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

Increase in age resulted in increased apparent oral clearance (CL/F) (58% increase in adolescents compared to children). Some of these differences could be explained by body weight differences among these populations. This suggests that subjects with higher body weight may have lower exposures of total methylphenidate at similar doses.

The pharmacokinetics of Methylphenidate Hydrochloride Extended Release Tablets has not been studied in children less than 6 years of age.

Renal Insufficiency

There is no experience with the use of Methylphenidate Hydrochloride Extended Release Tablets 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 PPA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of Methylphenidate Hydrochloride Extended Release Tablets.



Hepatic Insufficiency

There is no experience with the use of Methylphenidate Hydrochloride Extended Release Tablets in patients with hepatic insufficiency.

Clinical Studies

Methylphenidate Hydrochloride Extended Release Tablets demonstrated to be effective in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in 4 randomized, double-blind, placebo-controlled studies in children and adolescents who met the Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD.

Children

Three double blind, active- and placebo-controlled studies were conducted in 416 children aged 6 to 12. The controlled studies compared Methylphenidate Hydrochloride Extended Release Tablets given qd (18, 36, or 54 mg), methylphenidate given tid 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 Methylphenidate Hydrochloride Extended Release Tablets 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 Methylphenidate Hydrochloride Extended Release Tablets. The scores for Methylphenidate Hydrochloride Extended Release Tablets and placebo for the three studies are presented in Figure 2.



FIGURE 2
Mean (SEM) Community School Teacher IOWA Conners
Inattention/Overactivity Scores

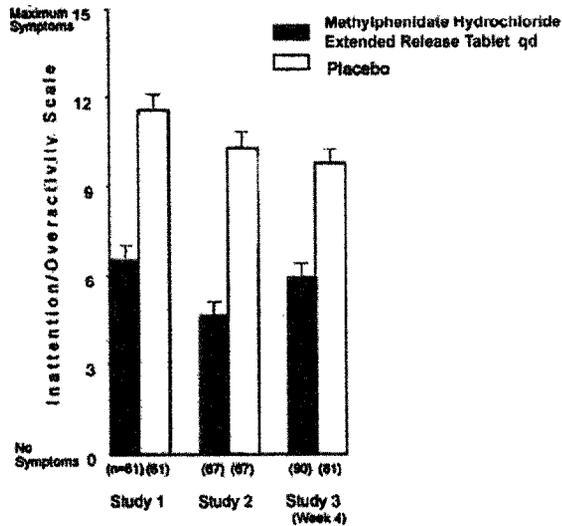


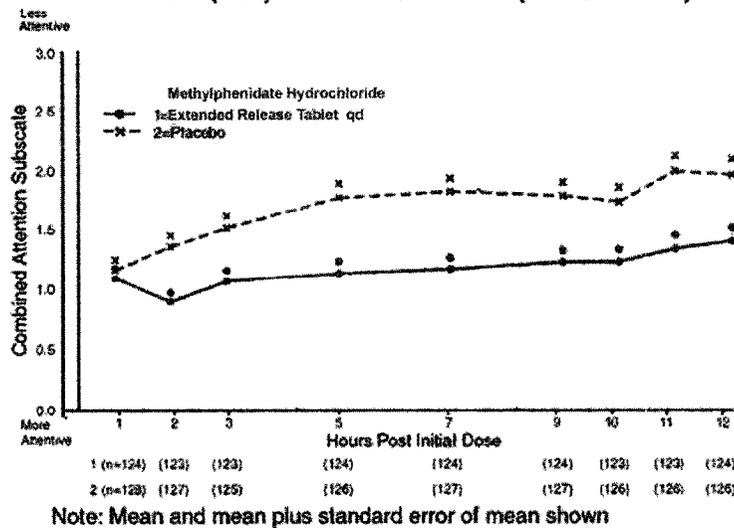
Figure 2: Mean Community School Teacher IOWA Conners Inattention/Overactivity Scores with Methylphenidate Hydrochloride Extended-Release Tablets once-daily (18, 36, or 54 mg) and placebo. Studies 1 and 2 involved a 3-way crossover of 1 week per treatment arm. Study 3 involved 4 weeks of parallel group 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 Methylphenidate Hydrochloride Extended Release Tablets versus placebo that were maintained through 12 hours after dosing. Figure 3 presents the laboratory school teacher SKAMP ratings for Methylphenidate Hydrochloride Extended Release Tablets and placebo.

*Swanson, Kotkin, Agler, M-Flynn and Pelham.



FIGURE 3
Laboratory School Teacher SKAMP Ratings
Mean (SEM) of Combined Attention (Studies 1 and 2)



Adolescents

In a randomized, double blind, multi-center, placebo-controlled trial (Study 4) involving 177 patients, Methylphenidate Hydrochloride Extended Release Tablets demonstrated to be effective in the treatment of ADHD in adolescents aged 13 to 18 at doses up to 72 mg/day (1.4 mg/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 Methylphenidate Hydrochloride Extended Release Tablets (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 Methylphenidate Hydrochloride Extended Release Tablets were significantly superior to placebo

INDICATION AND USAGE

Attention Deficit Hyperactivity Disorder (ADHD)

Methylphenidate Hydrochloride Extended Release Tablets are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of Methylphenidate Hydrochloride Extended Release Tablets in the treatment of ADHD was established in three controlled trials of children aged 6-12 and in one controlled trial in adolescents aged 13-17. All patients met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY).

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, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., 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; difficulty 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 presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

Methylphenidate Hydrochloride Extended Release Tablets are indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, and social) for patients with this syndrome. 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 Methylphenidate Hydrochloride Extended Release Tablets for long-term use, i.e., for more than 4 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Methylphenidate Hydrochloride Extended Release Tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).



CONTRAINDICATIONS

Agitation

Methylphenidate Hydrochloride Extended Release Tablets are contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate

Methylphenidate Hydrochloride Extended Release Tablets are contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma

Methylphenidate Hydrochloride Extended Release Tablets are contraindicated in patients with glaucoma.

Tics

Methylphenidate Hydrochloride Extended Release Tablets are contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see ADVERSE REACTIONS).

Monoamine Oxidase Inhibitors

Methylphenidate Hydrochloride Extended Release Tablets are contraindicated 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 PRECAUTIONS , Drug Interactions).

WARNINGS

Depression

Methylphenidate Hydrochloride Extended Release Tablets should not be used to treat severe depression.

Fatigue

Methylphenidate Hydrochloride Extended Release Tablets 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 (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.



Psychosis

Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

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 Methylphenidate Hydrochloride Extended Release Tablets are nondeformable and do not appreciably change in shape in the GI tract, Methylphenidate Hydrochloride Extended Release Tablets should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, Methylphenidate Hydrochloride Extended Release Tablets 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. Blood pressure should be monitored at appropriate intervals in patients taking Methylphenidate Hydrochloride Extended Release Tablets, especially patients with hypertension.

In the laboratory classroom clinical trials (Studies 1 and 2), both Methylphenidate Hydrochloride Extended Release Tablets and methylphenidate tid 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 the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with Methylphenidate Hydrochloride Extended Release Tablets and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for Methylphenidate Hydrochloride Extended Release Tablets and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively.



Visual Disturbance

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

Use in Children Under Six Years of Age

Methylphenidate Hydrochloride Extended Release Tablets should not be used in children under six years, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE

Methylphenidate Hydrochloride Extended Release Tablets 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.

PRECAUTIONS

Hematologic Monitoring

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Information for Patients

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

Patient information is printed at the end of this insert. To assure safe and effective use of Methylphenidate Hydrochloride Extended-Release Tablets, the information and instructions provided in the patient information section should be discussed with patients.

Drug Interactions

Because of possible effects on blood pressure, Methylphenidate Hydrochloride Extended Release Tablets should be used cautiously with pressor 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.

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

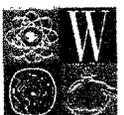
In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of Methylphenidate Hydrochloride Extended Release Tablets on a mg/kg and mg/m² basis, respectively. 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.

Methylphenidate did not cause any 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 Methylphenidate Hydrochloride Extended Release Tablets on a mg/kg and mg/m² 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 lifetime 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 Methylphenidate Hydrochloride Extended Release Tablets on a mg/kg and mg/m² 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/m² 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 Methylphenidate Hydrochloride Extended Release Tablets on a mg/kg and mg/m² basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPA in pregnant rats was 2 times that seen in trials in volunteers and patients with the maximum recommended dose of Methylphenidate Hydrochloride Extended Release Tablets based on the AUC.

There are no adequate and well-controlled studies in pregnant women. Methylphenidate Hydrochloride Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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

Pediatric Use

The safety and efficacy of Methylphenidate Hydrochloride Extended Release Tablets in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (see WARNINGS).

ADVERSE REACTIONS

The development program for Methylphenidate Hydrochloride Extended Release Tablets included exposures in a total of 2121 participants in clinical trials (1797 patients, 324 healthy adult subjects). These participants received Methylphenidate Hydrochloride Extended-Release Tablets 18, 36, 54 and/or 72 mg/day. Children, adolescents, and adults with ADHD were evaluated in four controlled clinical studies, three open-label clinical studies and two clinical pharmacology studies. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.



Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings in Clinical Trials with Methylphenidate Hydrochloride Extended Release Tablets

Adverse Events Associated with Discontinuation of Treatment

In the 4-week placebo-controlled, parallel-group trial in children (study 3) one Methylphenidate Hydrochloride Extended Release Tablet -treated patient (0.9%; 1/106) and one placebo-treated patient (1.0%; 1/99) discontinued due to an adverse event (sadness and increase in tics, respectively).

In the 2-week placebo-controlled phase of a trial in adolescents (Study 4), no Methylphenidate Hydrochloride Extended Release Tablet-treated patients (0%; 0/87) and 1 placebo-treated patient (1.1%; 1/90) discontinued due to an adverse event (increased mood irritability).

In the two open-label, long-term safety trials (Studies 5 and 6: one 24-month study in children aged 6 to 13 and one 9-month study in child, adolescent and adult patients treated with Methylphenidate Hydrochloride Extended Release Tablets) 6.7% (101/1514) of patients discontinued due to adverse events. These events with an incidence of >0.5% included: insomnia (1.5%), twitching (1.0%), nervousness (0.7%), emotional lability (0.7%), abdominal pain (0.7%), and anorexia (0.7%).

Treatment-Emergent Adverse Events Among Methylphenidate Hydrochloride Extended Release Tablets -Treated Patients

Table 4 enumerates, for a 4-week placebo-controlled, parallel-group trial (Study 3) in children with ADHD at Methylphenidate Hydrochloride Extended Release Tablets doses of 18, 36, or 54, mg/day, the incidence of treatment-emergent adverse events. The table includes only those events that occurred in 1% or more of patients treated with Methylphenidate Hydrochloride Extended Release Tablets where the incidence in patients treated with Methylphenidate Hydrochloride Extended Release Tablets was greater than the incidence in placebo-treated patients.



The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 4
Incidence of Treatment-Emergent Events¹ in a 4-Week
Placebo-Controlled Clinical Trial of
Methylphenidate Hydrochloride Extended Release Tablets In
Children

Body System	Preferred Term	Methylphenidate Hydrochloride Extended Release Tablet (n=106)	Placebo (n= 99)
General	Headache	14 %	10 %
	Abdominal pain (stomachache)	7 %	1 %
Digestive	Vomiting	4 %	3 %
	Anorexia (loss of appetite)	4 %	0 %
Nervous	Dizziness	2 %	0 %
	Insomnia	4 %	1 %
Respiratory	Upper Respiratory Tract Infection	8 %	5 %
	Cough Increased	4 %	2 %
	Pharyngitis	4 %	3 %
	Sinusitis	3 %	0 %

¹ Events, regardless of causality, for which the incidence for patients treated with Methylphenidate Hydrochloride Extended Release Tablets was at least 1% and greater than the incidence among placebo-treated patients. Incidence greater than 1% has been rounded to the nearest whole number.

Table 5 lists the incidence of treatment-emergent adverse events for a 2-week placebo-controlled trial (Study 4) in adolescents with ADHA at Methylphenidate Hydrochloride Extended Release Tablets doses of 8, 36, 54 or 72 mg/day.



TABLE 5
**Incidence of Treatment-Emergent Events ¹ in a 2-Week Placebo-
 Controlled Clinical Trial of Methylphenidate Hydrochloride
 Extended Release Tablets in Adolescents**

Body System	Preferred Term	Methylphenidate Hydrochloride Extended Release Tablet (n=87)	Placebo (n=90)
General	Accidental injury	6 %	3 %
	Fever	3 %	0 %
	Headache	9 %	8 %
Digestive	Anorexia	2 %	0 %
	Diarrhea	2 %	0 %
	Vomiting	3 %	0 %
Nervous	Insomnia	5 %	0 %
Respiratory	Pharyngitis	2 %	1 %
	Rhinitis	3 %	2 %
Urogenital	Dysmenorrhea	2 %	0 %

¹ Events, regardless of causality, for which the incidence for patients treated with Methylphenidate Hydrochloride Extended Release Tablets was at least 2% and greater than the incidence among placebo-treated patients. Incidence greater than 1% has been rounded to the nearest whole number.

Tics

In a long-term uncontrolled study (n=432 children), the cumulative incidence of new onset of tics was 9% after 27 months of treatment with Methylphenidate Hydrochloride Extended Release Tablets.

In a second uncontrolled study (n=682 children) the cumulative incidence of new onset tics was about 1% (9/682 children). The treatment period was up to 9 months with mean treatment duration of 7.2 months.

Adverse Events with Other Methylphenidate Hydrochloride Extended Release Tablets Products

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported.



Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten year old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Methylphenidate Hydrochloride Extended Release Tablets, like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

Abuse, Dependence, and Tolerance

See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE

Signs and Symptoms

Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Recommended 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 hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for Methylphenidate Hydrochloride Extended Release Tablets overdose has not been established.

The prolonged release of methylphenidate from Methylphenidate Hydrochloride Extended Release Tablets should be considered when treating patients with overdose.

Poison Control Center

As with the management of all overdose, 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 overdose with methylphenidate.

DOSAGE AND ADMINISTRATION

Methylphenidate Hydrochloride Extended Release Tablets should be administered orally once daily in the morning with or without food.

Methylphenidate Hydrochloride Extended Release Tablets must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed (see PRECAUTIONS: Information for Patients).

Based on an assessment of clinical benefit and tolerability, doses may be increased at weekly intervals for patients who have not achieved an optimal response at a lower dose.

Patients New to Methylphenidate

The recommended starting dose of Methylphenidate Hydrochloride Extended Release Tablets for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily.

Patient Age	Recommended Starting Dose	Maximum Dosage
Children 6-12 years of age	18 mg/day	54 mg/day
Adolescents 13-17 years of age	18 mg/day	72 mg/day not to exceed 2 mg/kg/day

Patients Currently Using Methylphenidate

The recommended dose of Methylphenidate Hydrochloride Extended-Release Tablets for patients who are currently taking methylphenidate bid or tid at doses of 10 to 45 mg/day is provided in Table 6. Dosing recommendations are based on current dose regimen and clinical judgment.



Initial conversion dosage should not exceed 54 mg daily. After conversion, dosages may be adjusted to a maximum of 72 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

TABLE 6
Recommended Dose Conversion from
Methylphenidate Regimens to Methylphenidate Hydrochloride
Extended Release Tablets

Previous Methylphenidate Daily Dose	Recommended CONCERTA [®] Starting Dose
5 mg Methylphenidate bid or tid	18 mg q am
10 mg Methylphenidate bid or tid	36 mg q am
15 mg Methylphenidate bid or tid	54 mg q am

Other methylphenidate regimens: Clinical judgment should be used when selecting the starting dose.

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

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 Methylphenidate Hydrochloride Extended-Release Tablets. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods.

Nevertheless, the physician who elects to use Methylphenidate Hydrochloride Extended Release Tablets 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.



HOW SUPPLIED

Methylphenidate Hydrochloride Extended Release Tablets are available in a 72 mg dosage strength. A description of the packaging will be provided in the ANDA.

72 mg XXX count bottle NDC XXXXX-XXX-XX

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from humidity.

REFERENCE

American Psychiatric Association. Diagnosis and Statistical Manual of Mental Disorders. 4th ed. Washington DC: American Psychiatric Association 1994.

Rx Only.

INFORMATION FOR PATIENTS TAKING METHYLPHENIDATE HYDROCHLORIDE EXTENDED RELEASE TABLETS OR THEIR PARENTS OR CAREGIVERS

Methylphenidate Hydrochloride Extended Release Tablets CII

This information is for patients taking Methylphenidate Hydrochloride Extended Release Tablets CII for the treatment of Attention Deficit Hyperactivity Disorder, or their parents or caregivers.

Please read this before you start taking Methylphenidate Hydrochloride Extended Release Tablets. Remember, this information does not take the place of your doctor's instructions. If you have any questions about this information or about Methylphenidate Hydrochloride Extended Release Tablets, talk to your doctor or pharmacist.

What are Methylphenidate Hydrochloride Extended Release Tablets?

Methylphenidate Hydrochloride Extended Release Tablets are a once-a-day treatment for Attention Deficit Hyperactivity Disorder, or ADHD. Methylphenidate Hydrochloride Extended Release Tablets contains the drug methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 30 years. Methylphenidate Hydrochloride Extended Release Tablets are taken by mouth, once each day in the morning.



What is Attention Deficit Hyperactivity Disorder?

ADHD has three main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all three types of symptoms.

Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis.

How do Methylphenidate Hydrochloride Extended Release Tablets work?

Part of the Methylphenidate Hydrochloride Extended Release Tablet dissolves right after you swallow it in the morning, giving you an initial dose of methylphenidate. The remaining drug is slowly released during the day to continue to help lessen the symptoms of ADHD. Methylphenidate, the active ingredient in Methylphenidate Hydrochloride Extended Release Tablets, helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Who should NOT take Methylphenidate Hydrochloride Extended Release Tablets?

You should NOT take Methylphenidate Hydrochloride Extended Release Tablets if:

- You have significant anxiety, tension, or agitation since Methylphenidate Hydrochloride Extended Release Tablets may make these conditions worse.
- You are allergic to methylphenidate or any of the other ingredients in Methylphenidate Hydrochloride Extended Release Tablets
- You have glaucoma, an eye disease.
- You have tics or Tourette's syndrome, or a family history of Tourette's syndrome.

Talk to your doctor if you believe any of these conditions apply to you.

How should I take Methylphenidate Hydrochloride Extended Release Tablets?

Do not chew, crush, or divide the tablets. Swallow Methylphenidate Hydrochloride Extended Release Tablets whole with the help of water or other liquids, such as milk or juice.



Take Methylphenidate Hydrochloride Extended Release Tablets once each day in the morning.

You may take Methylphenidate Hydrochloride Extended Release Tablets before or after you eat.

Take the dose prescribed by your doctor. Your doctor may adjust the amount of drug you take until it is right for you. From time to time, your doctor may interrupt your treatment to check your symptoms while you are not taking the drug.

What are the possible side effects of Methylphenidate Hydrochloride Extended Release Tablets?

In the clinical studies with patients using Methylphenidate Hydrochloride Extended Release Tablets the most common side effects were headache, stomach pain, sleeplessness, and decreased appetite. Other side effects seen with methylphenidate, the active ingredient in Methylphenidate Hydrochloride Extended Release Tablets, include nausea, vomiting, dizziness, nervousness, tics, allergic reactions, increased blood pressure and psychosis (abnormal thinking or hallucinations).

This is not a complete list of possible side effects. Ask your doctor about other side effects. If you develop any side effect, talk to your doctor.

What must I discuss with my doctor before taking Methylphenidate Hydrochloride Extended Release Tablets

Talk to your doctor before taking Methylphenidate Hydrochloride Extended Release Tablets if you:

Are being treated for depression or have symptoms of depression such as feelings of sadness, worthlessness, and hopelessness.

Have motion tics (hard-to-control, repeated twitching of any parts of your body) or verbal tics (hard-to-control repeating of sounds or words).

Have someone in your family with motion tics, verbal tics, or Tourette's syndrome.

Have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis.

Have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms).

Have high blood pressure.

Have a narrowing or blockage of your gastrointestinal tract (your esophagus, stomach, or small or large intestine).

Tell your doctor immediately if you develop any of the above conditions or symptoms while taking Methylphenidate Hydrochloride Extended-Release Tablets.



Can I take Methylphenidate Hydrochloride Extended Release Tablets with other medicines?

Tell your doctor about all medicines that you are taking. Your doctor should decide whether you can take Methylphenidate Hydrochloride Extended Release Tablets with other medicines. These include:

Other medicines that a doctor has prescribed.

Medicines that you buy yourself without a prescription.

Any herbal remedies that you may be taking.

You should not take Methylphenidate Hydrochloride Extended Release Tablets with monoamine oxidase (MAO) inhibitors.

While on Methylphenidate Hydrochloride Extended Release Tablets, do not start taking a new medicine or herbal remedy before checking with your doctor.

Methylphenidate Hydrochloride Extended Release Tablets may change the way your body reacts to certain medicines. These include medicines used to treat depression, prevent seizures, or prevent blood clots (commonly called "blood thinners"). Your doctor may need to change your dose of these medicines if you are taking them with Methylphenidate Hydrochloride Extended Release Tablets.

Other Important Safety Information

Abuse of methylphenidate can lead to dependence.

Tell your doctor if you have ever abused or been dependent on alcohol or drugs, or if you are now abusing or dependent on alcohol or drugs.

Before taking Methylphenidate Hydrochloride Extended Release Tablets, tell your doctor if you are pregnant or plan on becoming pregnant. If you take methylphenidate, it may be in your breast milk. Tell your doctor if you are nursing a baby.

Tell your doctor if you have blurred vision when taking Methylphenidate Hydrochloride Extended Release Tablets.

Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate in children. Your doctor will be carefully watching your height and weight. If you are not growing or gaining weight as your doctor expects, your doctor may stop your Methylphenidate Hydrochloride Extended Release Tablets treatment.



Call your doctor immediately if you take more than the amount of Methylphenidate Hydrochloride Extended Release Tablets prescribed by your doctor.

What else should I know about Methylphenidate Hydrochloride Extended Release Tablets?

Methylphenidate Hydrochloride Extended Release Tablets have not been studied in children under 6 years of age.

The Methylphenidate Hydrochloride Extended Release Tablets do not dissolve completely after all the drug has been released, and you may sometimes notice it in your stool. This is normal.

Methylphenidate Hydrochloride Extended Release Tablets may be a part of your overall treatment for ADHD. Your doctor may also recommend that you have counseling or other therapy.

As with all medicines, never share Methylphenidate Hydrochloride Extended Release Tablets with anyone else and take only the number of Methylphenidate Hydrochloride Extended Release Tablets prescribed by your doctor.

Methylphenidate Hydrochloride Extended Release Tablets should be stored in a safe place at room temperature (between 59°-86° F). Do not store this medicine in hot, damp, or humid places.

Keep out of the reach of children.

For more information call (phone number and website to be provided with ANDA submission).

Manufacturing Information to be included with ANDA submission.

