

METADATE[®] CD EXTENDED-RELEASE CAPSULES
ATTACHMENT TO NDA 21-259/S-001 APPROVAL LETTER

Once Daily
Metadate[®] CD
(methylphenidate HCl, USP)
Extended-Release Capsules CII

Rx Only

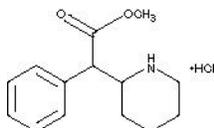
R549B
Rev. ~~XX/XX~~ 1/02

DESCRIPTION:

METADATE CD is a central nervous system (CNS) stimulant. METADATE CD contains 20 mg of methylphenidate hydrochloride for oral administration. The extended-release capsules comprise both immediate-release (IR) and extended-release (ER) beads such that 30% of the dose (6 mg) is provided by the IR component and 70% of the dose (14 mg) is provided by the ER component.

Chemically, methylphenidate HCl is *d,l* (racemic) -*threo*-methyl α -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

METADATE CD also contains the following inert ingredients: Sugar spheres, povidone, hydroxypropylmethylcellulose and polyethylene glycol, ethylcellulose aqueous dispersion, dibutyl sebacate, gelatin, titanium dioxide, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY:

Pharmacodynamics:

Methylphenidate HCl is a central nervous system (CNS) stimulant.

The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the *d*- and *l*-threo enantiomers. The *d*-threo enantiomer is more pharmacologically active than the *l*-threo enantiomer.

Pharmacokinetics:

The pharmacokinetics of the METADATE CD methylphenidate hydrochloride formulation have been studied in healthy adult volunteers and in children with attention deficit hyperactivity disorder (ADHD).

Absorption and Distribution:

Methylphenidate is readily absorbed. METADATE CD has a plasma/time concentration profile showing two phases of drug release with a sharp, initial slope similar to a methylphenidate immediate-release tablet, and a second rising portion approximately three hours later, followed by a gradual decline. (See Figure 1 below.)

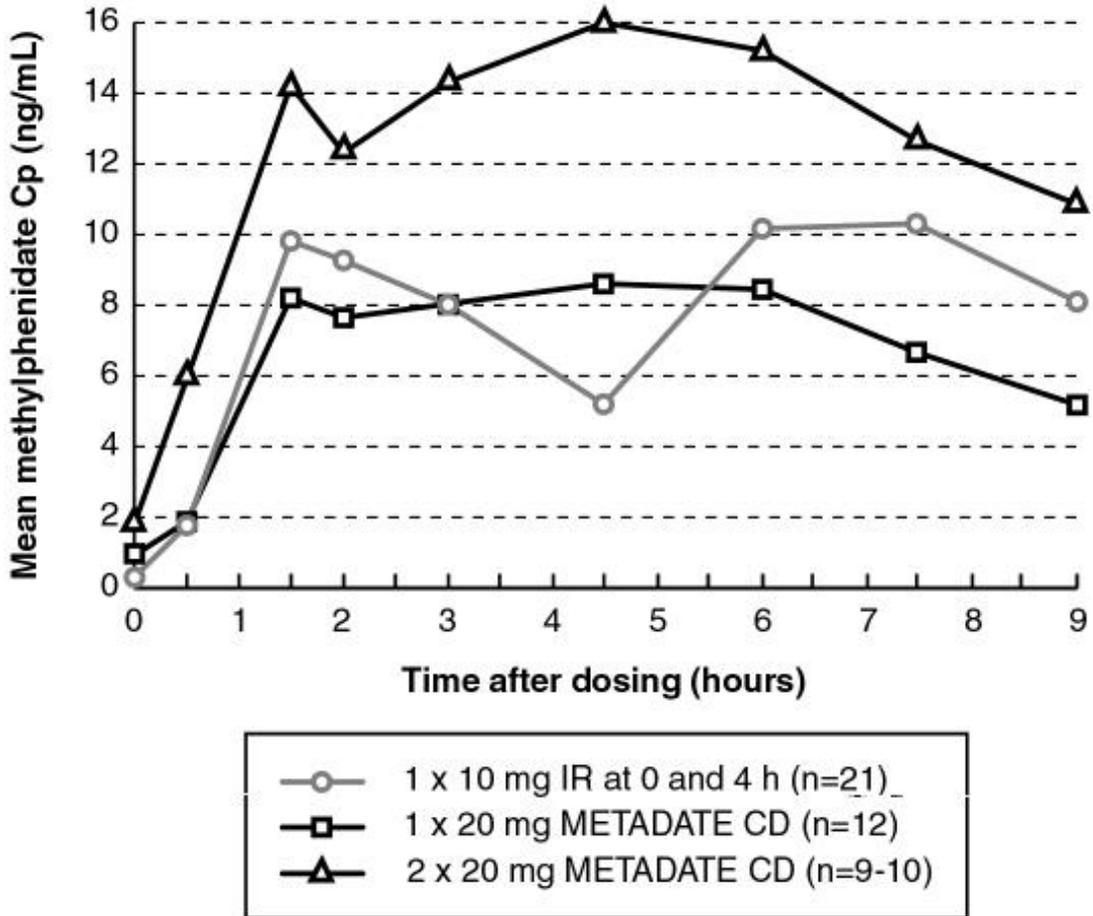
Comparison of Immediate Release (IR) and METADATE CD Formulations After Repeated Doses of Methylphenidate HCl in Children with ADHD:

METADATE CD was administered as repeated once-daily doses of 20 mg or 40 mg to children aged 7-12 years with ADHD for one week. After a dose of 20 mg, the mean (\pm SD) early C_{\max} was 8.6 (\pm 2.2) ng/mL, the later C_{\max} was 10.9 (\pm 3.9)* ng/mL and AUC_{0-9h} was 63.0 (\pm 16.8) ng•h/mL. The corresponding values after a 40 mg dose were 16.8 (\pm 5.1) ng/mL, 15.1 (\pm 5.8)* ng/mL and 120 (\pm 39.6) ng•h/mL, respectively. The early peak concentrations (median) were reached about 1.5 hours after dose intake, and the second peak concentrations (median) were reached about 4.5 hours after dose intake. The means for C_{\max} and AUC following a dose of 20 mg were slightly lower than those seen with 10 mg of the immediate-release formulation, dosed at 0 and 4 hours.

*25-30% of the subjects had only one observed peak (C_{\max}) concentration of methylphenidate.

FIGURE 1

Comparison of Immediate Release (IR) and METADATE CD Formulations After Repeated Doses of Methylphenidate HCl in Children with ADHD



Dose Proportionality:

Following single oral doses of 10-60 mg methylphenidate free base as a solution given to ten healthy male volunteers, C_{\max} and AUC increased proportionally with increasing doses. After the 60 mg dose, t_{\max} was reached 1.5 hours post-dose, with a mean C_{\max} of 31.8 ng/mL (range 24.7 - 40.9 ng/mL).

Following one week of repeated once-daily doses of 20 mg or 40 mg METADATE CD to children aged 7-12 years with ADHD, C_{\max} and AUC were proportional to the administered dose.

Food Effects:

In a study in adult volunteers to investigate the effects of a high-fat meal on the bioavailability of a dose of 40 mg, the presence of food delayed the early peak by approximately 1 hour (range - 2 to 5 hours delay). The plasma levels rose rapidly following the food-induced delay in absorption. Overall, a high fat meal increased the C_{\max} of METADATE CD by about 30% and AUC by about 17%, on average (see DOSAGE and ADMINISTRATION).

After a single dose, the bioavailability (C_{\max} and AUC) of methylphenidate in 26 healthy adults was unaffected by sprinkling the capsule contents on applesauce as compared to the intact capsule. This finding demonstrates that a 20 mg METADATE CD Capsule, when opened and sprinkled on one tablespoon of applesauce, is bioequivalent to the intact capsule.'

Metabolism and Excretion:

In humans, methylphenidate is metabolized primarily via deesterification to alpha-phenyl-piperidine acetic acid (ritalinic acid). The metabolite has little or no pharmacologic activity.

In vitro studies showed that methylphenidate was not metabolized by cytochrome P450 isoenzymes, and did not inhibit cytochrome P450 isoenzymes at clinically observed plasma drug concentrations.

The mean terminal half-life ($t_{1/2}$) of methylphenidate following administration of METADATE CD ($t_{1/2}$ =6.8h) is longer than the mean terminal $t_{1/2}$ following administration of methylphenidate hydrochloride immediate-release tablets ($t_{1/2}$ =2.9h) and methylphenidate hydrochloride sustained-release tablets ($t_{1/2}$ =3.4h) in healthy adult volunteers. This suggests that the elimination process observed for METADATE CD is controlled by the release rate of methylphenidate from the extended-release formulation, and that the drug absorption is the rate-limiting process.

Special Populations:

Gender: The pharmacokinetics of methylphenidate after a single dose of METADATE CD were similar between adult men and women.

Race: The influence of race on the pharmacokinetics of methylphenidate after METADATE CD administration has not been studied.

Age: The pharmacokinetics of methylphenidate after METADATE CD administration have not been studied in children less than 6 years of age.

Renal and Hepatic Insufficiency:

~~The pharmacokinetics of methylphenidate after METADATE CD administration has not been studied in patients with renal or hepatic insufficiency.~~

Renal Insufficiency

There is no experience with the use of METADATE ® CD 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 ritalinic acid. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of METADATE ® CD.

Hepatic Insufficiency

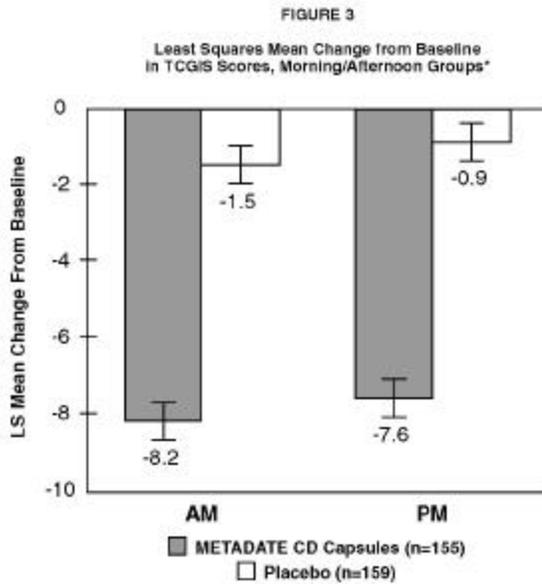
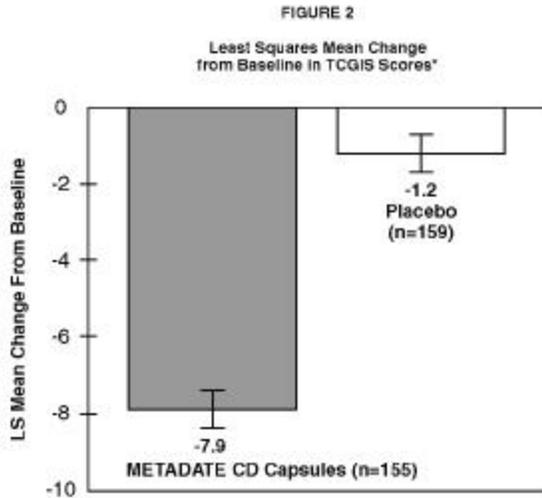
There is no experience with the use of METADATE ® CD in patients with hepatic insufficiency.

CLINICAL STUDIES:

METADATE CD was evaluated in a double-blind, parallel-group, placebo-controlled trial in which 321 untreated or previously treated pediatric patients with a DSM-IV diagnosis of attention deficit hyperactivity disorder (ADHD), 6 to 15 years of age, received a single morning dose for up to 3 weeks. Patients were required to have the combined or predominantly hyperactive-impulsive subtype of ADHD; patients with the predominantly inattentive subtype were excluded. Patients randomized to the METADATE CD group received 20 mg daily for the first week. Their dosage could be increased weekly to a maximum of 60 mg by the third week, depending on individual response to treatment.

The patient's regular school teacher completed the teachers' version of the Conners' Global Index Scale (TCGIS), a scale for assessing ADHD symptoms, in the morning and again in the afternoon on three alternate days of each treatment week. The change from baseline of the overall average (i.e., an average of morning and afternoon scores over 3 days) of the total TCGIS scores during the last week of treatment was analyzed as the primary efficacy parameter. Patients treated with METADATE CD showed a statistically significant

improvement in symptom scores from baseline over patients who received placebo. (See Figure 2.) Separate analyses of TCGIS scores in the morning and afternoon revealed superiority in improvement with METADATE CD over placebo during both time periods. (See Figure 3.) This demonstrates that a single morning dose of METADATE CD exerts a treatment effect in both the morning and the afternoon.



* FIGURES 2 & 3: Last observation carried forward analysis at week 3. Error bars represent the standard error of the mean.

INDICATION AND USAGE:
Attention Deficit Hyperactivity Disorder (ADHD):

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

The efficacy of METADATE CD in the treatment of ADHD was established in one controlled trial of children aged 6 to 15 who 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 Types 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 not only of medical but of 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:

METADATE CD 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 METADATE CD for long-term use, i.e., for more than 3 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use

METADATE CD for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE and ADMINISTRATION).

CONTRAINDICATIONS:**Agitation:**

METADATE CD is contraindicated in patients with marked anxiety, tension and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate:

METADATE CD is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma:

METADATE CD is contraindicated in patients with glaucoma.

Tics:

METADATE CD is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome. (see ADVERSE REACTIONS).

Monoamine Oxidase Inhibitors:

METADATE CD is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS:**Depression:**

METADATE CD should not be used to treat severe depression.

Fatigue:

METADATE CD 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.

Hypertension and other Cardiovascular Conditions:

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in patients taking METADATE CD, especially patients with hypertension. Studies of methylphenidate have shown modest increases of resting pulse

and systolic and diastolic blood pressure. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or hyperthyroidism.

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:

METADATE CD should not be used in children under six years, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE: METADATE CD 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 instructed to take one dose in the morning before breakfast. They should be instructed that the capsule must be swallowed whole, and not opened, crushed, or chewed.~~
Patients should be instructed to take one dose in the morning before breakfast. The patients should be instructed that the capsule may be swallowed whole, or alternatively, the capsule may be opened and the capsule contents sprinkled onto a small amount (tablespoon) of applesauce and given immediately, and not stored for future use. The capsules and the capsule contents must not be crushed or chewed.

Patient information is printed along with this insert. To assure safe and effective use of METADATE CD, the information and instructions provided in the patient information section should be discussed with patients.

Drug Interactions:

Because of possible effects on blood pressure, METADATE CD 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 METADATE CD 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 METADATE CD 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 in 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 METADATE CD 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 teratogenicity at an oral dose of 58 mg/kg/day. However, this dose, which caused some maternal toxicity, resulted in decreased postnatal pup weights and survival when given to the dams from day one of gestation through the lactation period. This dose is approximately 30 fold and 6 fold the maximum recommended human dose of METADATE CD on a mg/kg and mg/m² basis, respectively.

There are no adequate and well-controlled studies in pregnant women. METADATE CD 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 METADATE CD is administered to a nursing woman.

Pediatric Use:

The safety and efficacy of METADATE CD 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 premarketing development program for METADATE CD included exposures in a total of 228 participants in clinical trials (188 pediatric patients with ADHD, 40 healthy adult subjects). These participants received METADATE CD 20, 40, and/or 60 mg/day. The 188 patients (ages 6 to 15) were evaluated in one controlled clinical study, one controlled, crossover clinical study, and one uncontrolled clinical study. Safety data on all patients are included in the discussion that follows. 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 METADATE CD:

Adverse Events Associated with Discontinuation of Treatment:

In the 3-week placebo-controlled, parallel-group trial, two METADATE CD-treated patients (1%) and no placebo-treated patients discontinued due to an adverse event (rash and pruritus; and headache, abdominal pain, and dizziness, respectively).

Adverse Events Occurring at an Incidence of 5% or more Among METADATE CD-Treated Patients:

Table 1 enumerates, for a pool of the three studies in pediatric patients with ADHD, at METADATE CD doses of 20, 40, or 60 mg/day, the incidence of treatment-emergent adverse events. One study was a 3-week placebo-controlled, parallel-group trial, one study was a controlled, crossover trial, and the third study was an open titration trial. The table includes only those events that occurred in 5% or more of patients treated with METADATE CD where the incidence in patients treated with METADATE CD 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 1
Incidence of Treatment-Emergent Events¹ in a Pool of 3-4 Week Clinical Trials of METADATE CD

Body System	Preferred Term	METADATE CD (n=188)	Placebo (n=190)
General	Headache	12%	8%
	Abdominal pain (stomach ache)	7%	4%
Digestive System	Anorexia (loss of appetite)	9%	2%
Nervous System	Insomnia	5%	2%

¹:Events, regardless of causality, for which the incidence for patients treated with METADATE CD was at least 5% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Adverse Events with Other Methylphenidate HCl 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 reported, 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:**

METADATE CD, 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 METADATE CD overdose has not been established.

The prolonged release of methylphenidate from METADATE CD 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:

METADATE CD is administered once daily in the morning, before breakfast.

~~METADATE CD must be swallowed whole with the aid of liquids, and must not be opened, crushed or chewed. (See PRECAUTIONS: Information for Patients.)~~

METADATE CD may be swallowed whole with the aid of liquids, or alternatively, the capsule may be opened and the capsule contents sprinkled onto a small amount (tablespoon) of applesauce and given immediately, and not stored for future use. Drinking some fluids, e.g. water, should follow the intake of the sprinkles with applesauce. The capsules and the capsule contents must not be crushed or chewed. (See PRECAUTIONS: Information for Patients).

Dosage should be individualized according to the needs and responses of the patient.

Initial Treatment:

The recommended starting dose of METADATE CD is 20 mg once daily.

Dosage may be adjusted in weekly 20 mg increments to a maximum of 60 mg/day taken once daily in the morning, depending upon tolerability and degree of efficacy observed. Daily dosage above 60 mg is not recommended.

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 METADATE CD. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use METADATE CD 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:

METADATE CD (methylphenidate HCl, USP) Extended-Release Capsules are available as 20 mg blue and white capsules. The capsule is printed with "MEDEVA 575" in white letters on the blue cap, and "20 mg" in black letters on the white body of the capsule.

NDC 53014-575-30 Dose Pack of 30 Capsules

PHARMACIST: Dispense only in current dose pack.

Store at 25°C (77°F): excursions permitted to 15° - 30°C (59° - 86°F) [See USP Controlled Room Temperature]

Keep out of the reach of children.

Reference

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

Marketed by:

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Vandalia, Ohio 45377 USA

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Rev. X/XX R549

INFORMATION FOR PATIENTS TAKING METADATE® CD OR THEIR PARENTS OR CAREGIVERS

**Once Daily
Metadate® CD
(methylphenidate HCl, USP)
Extended-Release Capsules CII**

This information is for patients or their parents or caregivers taking METADATE CD Capsules for the treatment of Attention Deficit Hyperactivity Disorder.

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

What is METADATE® CD?

METADATE CD is a once-a-day treatment for Attention Deficit Hyperactivity Disorder, or ADHD. METADATE CD contains the drug methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 30 years. METADATE CD is taken by mouth, once each day in the morning, before breakfast.

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 does METADATE® CD work?

The METADATE CD capsule 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 METADATE

CD, helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Who should NOT take METADATE® CD?

You should NOT take METADATE CD if:

- You have significant anxiety, tension, or agitation since METADATE CD may make these conditions worse.
- You are allergic to methylphenidate or any of the other ingredients in METADATE CD.
- 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 METADATE® CD?

~~Do not chew, crush, or open the capsules. Swallow METADATE CD capsules whole with the help of water or other liquids, such as milk or juice.~~

Do not chew or crush the capsules or the beads inside the capsule. Swallow the METADATE CD Capsules whole with the help of water or other liquids, such as whole milk or juice. Alternatively, the capsule may be opened and the capsule contents sprinkled onto a small amount (tablespoon) of applesauce and taken immediately (do not store for future use) without chewing. Take a drink of water after the sprinkles with applesauce have been swallowed.

Take METADATE CD once each day in the morning, before breakfast.

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 METADATE® CD?

In the clinical studies with patients using METADATE CD, the most common side effects were headache, stomach pain, sleeplessness, and decreased appetite. Other side effects seen with methylphenidate, the active ingredient in METADATE CD, 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 METADATE® CD?

Talk to your doctor ***before*** taking METADATE CD 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.

Tell your doctor ***immediately*** if you develop any of the above conditions or symptoms while taking METADATE CD.

Can I take METADATE® CD with other medicines?

Tell your doctor about ***all*** medicines that you are taking or intend to take. Your doctor should decide whether you can take METADATE CD with other medicines. These include:

- Other medicines that a doctor has prescribed.
- All medicines that you buy yourself without a prescription.
- Any herbal remedies that you may be taking.

You should not take METADATE CD with monoamine oxidase (MAO) inhibitors.

While on METADATE CD, do not start taking a new medicine or herbal remedy before checking with your doctor.

METADATE CD 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 METADATE CD.

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 METADATE CD, 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 METADATE CD.

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 METADATE CD treatment.

Call your doctor ***immediately*** if you take more than the amount of METADATE CD prescribed by your doctor.

What else should I know about METADATE[®] CD?

METADATE CD has not been studied in children under 6 years of age.

METADATE CD 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 METADATE CD with anyone else and take only the number of METADATE CD Capsules prescribed by your doctor.

METADATE CD should be stored in a safe place at room temperature (between 59°-86°F).

Keep out of the reach of children.

For more information call 1-888-METADATE (1-888-638-2328).

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/s/

Russell Katz

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