

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-278**

**APPROVED DRAFT LABELING**

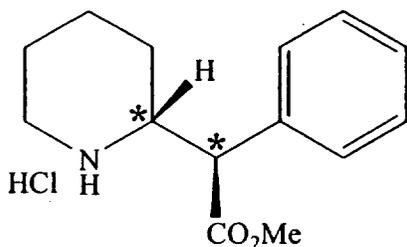
## TRADENAME

### Dexmethylphenidate hydrochloride tablets

Rx only

## DESCRIPTION

TRADENAME (Dexmethylphenidate HCl) is the *d-threo*- enantiomer of racemic methylphenidate hydrochloride, which is a 50/50 mixture of the *d-threo*- and *l-threo*- enantiomers. TRADENAME is a central nervous system (CNS) stimulant, available in three tablet strengths. Each tablet contains dexmethylphenidate hydrochloride 2.5, 5, or 10 mg for oral administration. Dexmethylphenidate hydrochloride is methyl  $\alpha$ -phenyl-2-piperidineacetate hydrochloride, (R,R')-(+)-. Its empirical formula is  $C_{14}H_{19}NO_2 \cdot HCl$ . Its molecular weight is 269.77 and its structural formula is:



Note: \* = asymmetric carbon centers

Dexmethylphenidate hydrochloride is a white to off white 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.

TRADENAME also contains the following inert ingredients: pregelatinized starch, lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, magnesium stearate, and FD&C Blue No.1 #5516 aluminum lake (2.5 mg tablets), D&C Yellow Lake #10 (5 mg tablets); the 10 mg tablet contains no dye.

## CLINICAL PHARMACOLOGY

### Pharmacodynamics

Dexmethylphenidate hydrochloride is a central nervous system stimulant. TRADENAME, the more pharmacologically active enantiomer of the *d*- and *l*-enantiomers, 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. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known.

## Pharmacokinetics

### Absorption

Dexmethylphenidate hydrochloride is readily absorbed following oral administration of TRADENAME. In patients with ADHD, plasma dexmethylphenidate concentrations increase rapidly, reaching a maximum in the fasted state at about 1 to 1½ hours post-dose. No differences in the pharmacokinetics of TRADENAME were noted following single and repeated twice daily dosing, thus indicating no significant drug accumulation in children with ADHD.

When given to children as capsules in single doses of 2.5 mg, 5 mg, and 10 mg,  $C_{max}$  and  $AUC_{0-inf}$  of dexmethylphenidate were proportional to dose. In the same study, plasma dexmethylphenidate levels were comparable to those achieved following single *dl-threo*-methylphenidate HCl doses given as capsules in twice the total mg amount (equimolar with respect to TRADENAME).

### Food Effects

In a single dose study conducted in adults, coadministration of 2x10 mg TRADENAME with a high fat breakfast resulted in a dexmethylphenidate  $t_{max}$  of 2.9 hours post-dose as compared to 1.5 hours post-dose when given in a fasting state.  $C_{max}$  and  $AUC_{0-inf}$  were comparable in both the fasted and non-fasted states.

### Distribution

Plasma dexmethylphenidate concentrations in children decline exponentially following oral administration of TRADENAME.

### Metabolism and Excretion

In humans, dexmethylphenidate is metabolized primarily to *d*- $\alpha$ -phenyl-piperidine acetic acid (also known as *d*-ritalinic acid) by de-esterification. This metabolite has little or no pharmacological activity. There is little or no *in vivo* interconversion to the *l-threo*-enantiomer, based on a finding of minute levels of *l-threo*-methylphenidate being detectable in a few samples in only 2 of 58 children and adults. After oral dosing of radiolabeled racemic methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was ritalinic acid, accountable for approximately 80% of the dose.

*In vitro* studies showed that dexmethylphenidate did not inhibit cytochrome P450 isoenzymes.

The mean plasma elimination half-life of dexmethylphenidate is approximately 2.2 hours.

## Special Populations

### Gender

Pharmacokinetic parameters were similar for boys and girls (mean age 10 years).

In a single dose study conducted in adults, the mean dexamethylphenidate AUC<sub>0-inf</sub> values (adjusted for body weight) following single 2 x 10 mg doses of TRADENAME were 25-35% higher in adult female volunteers (n=6) compared to male volunteers (n=9). Both t<sub>max</sub> and t<sub>1/2</sub> were comparable for males and females.

### Race

There is insufficient experience with the use of TRADENAME to detect ethnic variations in pharmacokinetics.

### Age

The pharmacokinetics of dexamethylphenidate after TRADENAME administration have not been studied in children less than 6 years of age. When single doses of TRADENAME were given to children between the ages of 6 to 12 years and healthy adult volunteers, C<sub>max</sub> of dexamethylphenidate was similar, however children showed somewhat lower AUCs compared to the adults.

### Renal Insufficiency

There is no experience with the use of TRADENAME in patients with renal insufficiency. After oral administration of radiolabeled racemic 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 very little unchanged drug is excreted in the urine, renal insufficiency is expected to have little effect on the pharmacokinetics of TRADENAME.

### Hepatic Insufficiency

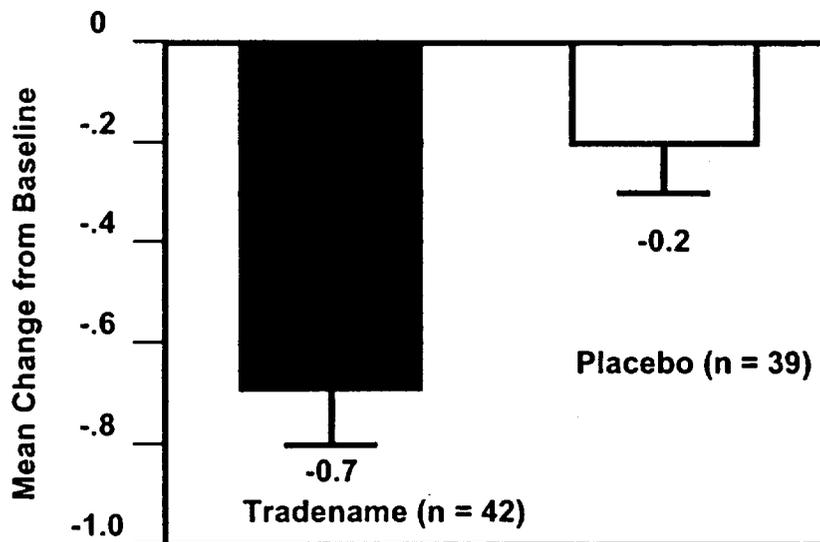
There is no experience with the use of TRADENAME in patients with hepatic insufficiency.  
(For Drug Interactions, see Precautions)

## Clinical Studies

TRADENAME was evaluated in two double-blind, parallel-group, placebo-controlled trials in untreated or previously treated patients aged 6 to 17 years old with a DSM-IV diagnosis of Attention Deficit Hyperactivity Disorder (ADHD). Both studies included all three subtypes of ADHD, i.e., Combined Type, Predominantly Inattentive Type, or Predominantly Hyperactive-Impulsive Type. While both children and adolescents were included, the sample was predominantly children, thus, the findings are most pertinent to this age group. In both studies, the primary comparison of interest was TRADENAME *versus* placebo.

TRADENAME (5, 10, or 20 mg/day total dose), *dl-threo*-methylphenidate HCl (10, 20, or 40 mg/day total dose), and placebo were compared in a multicenter, 4-week, parallel group study in n=132 patients. Patients took the study medication twice daily, 3.5 to 5.5 hours between doses. Treatment was initiated with the lowest dose, and doses could be doubled at weekly intervals, depending on clinical response and tolerability, up to the maximum dose. The change from baseline to week 4 of the averaged score (an average of two ratings during the week) of the teacher's version of the SNAP-ADHD Rating Scale, a scale for assessing ADHD symptoms, was the primary outcome. Patients treated with TRADENAME showed a statistically significant improvement in symptom scores from baseline over patients who received placebo.

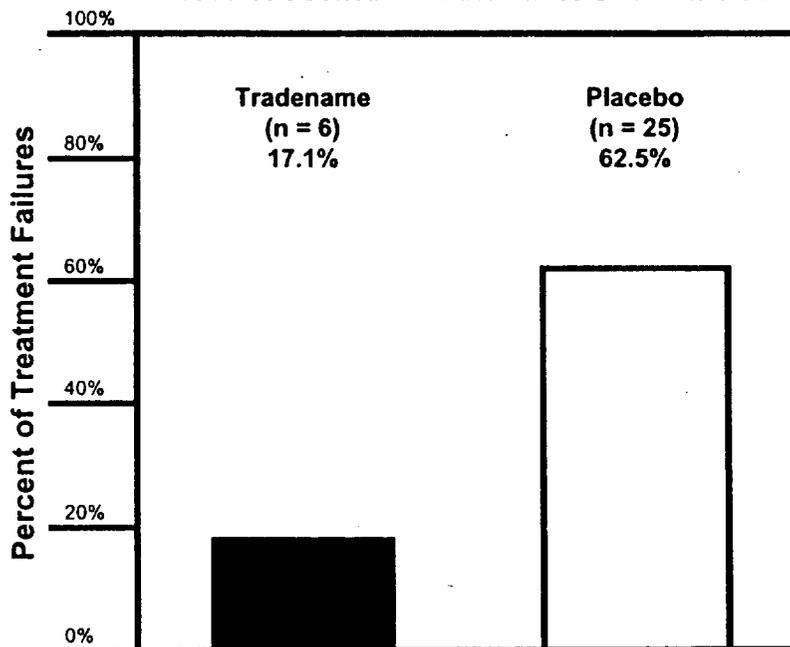
**Figure 1**  
**Mean Change from Baseline in Teacher SNAP-ADHD Scores**  
**in a 4-week Double-blind Placebo-controlled Study of**  
**TRADENAME\***



\*Figure 1: Error bars represent the standard error of the mean.

The other study, involving n=75 patients, was a multicenter, placebo-controlled, double-blind, 2-week treatment withdrawal study in children who were responders during a 6-week, open label initial treatment period. Children took study medication twice a day separated by a 3.5 to 5.5 hour interval. The primary outcome was proportion of treatment failures at the end of the 2-week withdrawal phase, where treatment failure was defined as a rating of 6 (much worse) or 7 (very much worse) on the Investigator Clinical Global Impression –Improvement (CGI-I). Patients continued on TRADENAME showed a statistically significant lower rate of failure over patients who received placebo.

**Figure 2**  
**Percent of Treatment Failures following a 2-week Double-blind Placebo-controlled Withdrawal of TRADENAME**



## INDICATION AND USAGE

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

The efficacy of TRADENAME in the treatment of ADHD was established in two controlled trials of patients aged 6 to 17 years of age who met DSM-IV criteria for ADHD (See Clinical Studies).

A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that cause 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 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**

TRADENAME 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 patients with this syndrome. Stimulants are not intended for use in the patient 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 patient’s symptoms.

### **Long-term Use**

The effectiveness of TRADENAME for long-term use, *i.e.*, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use TRADENAME for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see Dosage and Administration).

## **CONTRAINDICATIONS**

### **Agitation**

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

### **Hypersensitivity to Methylphenidate**

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

## **Glaucoma**

TRADENAME is contraindicated in patients with glaucoma.

## **Tics**

TRADENAME is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see Adverse Reactions).

## **Monoamine Oxidase Inhibitors**

TRADENAME 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**

TRADENAME should not be used to treat severe depression.

### **Fatigue**

TRADENAME should not be used for the prevention or treatment of normal fatigue states.

### **Long-Term Suppression of Growth**

Sufficient data on safety of long-term use of TRADENAME 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 children, 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 the absence of a history of seizures, and, very rarely, in the absence of a 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 all patients taking TRADENAME, especially those with hypertension.

In the placebo controlled studies, the mean pulse increase was 2-5 bpm for both TRADENAME and racemic methylphenidate compared to placebo, with mean increases of systolic and diastolic blood pressure of 2-3 mmHg, compared to placebo. 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 following use of methylphenidate. Difficulties with accommodation and blurring of vision have been reported.

## **Use in Children Under 6 Years of Age**

TRADENAME should not be used in children under 6 years, since safety and efficacy in this age group have not been established.

<p><b>DRUG DEPENDENCE:</b> TRADENAME 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 drug 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.</p>
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## **PRECAUTIONS**

### **Hematologic Monitoring**

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

### **Information for Patients**

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

### **Drug Interactions**

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension. Because of possible effects on blood pressure, TRADENAME should be used cautiously with pressor agents.

Human pharmacologic studies have shown that racemic 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 adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentration (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**

Lifetime carcinogenicity studies have not been carried out with dexamethylphenidate. In a lifetime carcinogenicity study carried out in B6C3F1 mice, racemic 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. 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.

Racemic methylphenidate did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day.

In a 24-week study of racemic methylphenidate in the transgenic mouse strain p53<sup>+/-</sup>, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Mice were fed diets containing the same concentrations as in the lifetime carcinogenicity study; the high-dose group was exposed to 60 to 74 mg/kg/day of racemic methylphenidate.

Dexamethylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma cell forward mutation assay, or the *in vivo* mouse bone marrow micronucleus test.

Racemic methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay, and was negative *in vivo* in the mouse bone marrow micronucleus assay. However, sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay of racemic methylphenidate in cultured Chinese Hamster Ovary (CHO) cells.

Racemic 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 of up to 160 mg/kg/day.

### **Pregnancy**

#### **Pregnancy Category C**

In studies conducted in rats and rabbits, dexamethylphenidate was administered orally at doses of up to 20 and 100 mg/kg/day, respectively, during the period of organogenesis. No evidence of teratogenic activity was found in either the rat or rabbit study; however, delayed fetal skeletal ossification was observed at the highest dose level in rats. When dexamethylphenidate was administered to rats throughout pregnancy and

lactation at doses of up to 20 mg/kg/day, postweaning body weight gain was decreased in male offspring at the highest dose, but no other effects on postnatal development were observed. At the highest doses tested, plasma levels (AUCs) of dexamethylphenidate in pregnant rats and rabbits were approximately 5 and 1 times, respectively, those in adults dosed with the maximum recommended human dose of 20 mg/day.

Racemic methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day throughout organogenesis.

Adequate and well-controlled studies in pregnant women have not been conducted. TRADENAME should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### **Nursing Mothers**

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

### **Pediatric Use**

The safety and efficacy of TRADENAME in children under 6 years old have not been established. Long-term effects of TRADENAME in children have not been well established (see Warnings).

## **ADVERSE REACTIONS**

The pre-marketing development program for TRADENAME included exposures in a total of 696 participants in clinical trials (684 patients, 12 healthy adult subjects). These participants received TRADENAME 5, 10, or 20 mg/day. The 684 ADHD patients (ages 6 to 17 years) were evaluated in two controlled clinical studies, two clinical pharmacology studies, and two uncontrolled long-term safety studies. Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, and results of physical examinations, vital sign and body weight measurements, and laboratory analyses.

Adverse events during exposure were primarily obtained 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 tabulations that follow, standard COSTART dictionary 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 TRADENAME

### Adverse Events Associated with Discontinuation of Treatment

No TRADENAME-treated patients discontinued due to adverse events in two placebo-controlled trials. Overall, 50 of 684 children treated with TRADENAME (7.3%) experienced an adverse event that resulted in discontinuation. The most common reasons for discontinuation were twitching (described as motor or vocal tics), anorexia, insomnia, and tachycardia (approximately 1% each).

### Adverse Events Occurring at an Incidence of 5% or More Among TRADENAME-Treated Patients

Table 1 enumerates treatment-emergent adverse events for two, placebo-controlled, parallel group trials in children with ADHD at TRADENAME doses of 5, 10, and 20 mg/day. The table includes only those events that occurred in 5% or more of patients treated with TRADENAME where the incidence in patients treated with TRADENAME was at least twice 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**  
**Treatment-emergent Adverse Events<sup>1</sup> Occurring During Double-Blind Treatment in Clinical Trials of TRADENAME**

<u>Body System</u>	<u>Preferred Term</u>	<u>TRADENAME (n=79)</u>	<u>Placebo (n=82)</u>
Body as a Whole	Abdominal Pain	15%	6%
	Fever	5%	1%
Digestive System	Anorexia	6%	1%
	Nausea	9%	1%

<sup>1</sup> Events, regardless of causality, for which the incidence for patients treated with TRADENAME was at least 5% and twice 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. 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 below may also occur.

Other reactions include:

Cardiac: angina, arrhythmia, palpitations, pulse increased or decreased

Gastrointestinal: nausea

Immune: hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura.

Nervous System: dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis

Vascular: blood pressure increased or decreased, cerebral arteritis and/or occlusion

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:

Blood/lymphatic: leukopenia and/or anemia

Hepato-biliary: abnormal liver function, ranging from transaminase elevation to hepatic coma

Psychiatric: transient depressed mood

Skin/subcutaneous: 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**

TRADENAME, 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 for TRADENAME overdose has not been established.

### **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**

TRADENAME is administered twice daily, at least 4 hours apart. TRADENAME may be administered with or without food.

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

### **Patients New to Methylphenidate**

The recommended starting dose of TRADENAME for patients who are not currently taking racemic methylphenidate, or for patients who are on stimulants other than methylphenidate, is 5 mg/day (2.5 mg twice daily).

Dosage may be adjusted in 2.5 to 5 mg increments to a maximum of 20 mg/day (10 mg twice daily). In general, dosage adjustments may proceed at approximately weekly intervals.

### **Patients Currently Using Methylphenidate**

For patients currently using methylphenidate, the recommended starting dose of TRADENAME is half the dose of racemic methylphenidate. The maximum recommended dose is 20 mg/day (10 mg twice daily).

### **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 TRADENAME. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use TRADENAME for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with periods 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 1-month period, the drug should be discontinued.

### **HOW SUPPLIED**

Tablets, D-shaped, embossed "D" on upper convex face and dosage strength on lower convex face

Tablets 2.5 mg - blue  
Bottles of 100..... NDC 0078-0380-05

Tablets 5 mg - yellow  
Bottles of 100..... NDC 0078-0381-05

Tablets 10 mg - white  
Bottles of 100..... NDC 0078-0382-05

Store at 25°C (77°F); excursions permitted 15-30°C (59-86°F).

[see USP Controlled Room Temperature]

Protect from light and moisture.

## **REFERENCE**

American Psychiatric Association. *Diagnosis and Statistical Manual of Mental Disorders*. 4<sup>th</sup> ed. Washington DC: American Psychiatric Association 1994.

Rx Only

Manufactured by Mikart , Inc. (Atlanta, GA) for Novartis Pharmaceutical Corporation.

## **INFORMATION FOR PATIENTS TAKING TRADENAME OR THEIR PARENTS OR CAREGIVERS**

### **TRADENAME**

**Dexmethylphenidate hydrochloride**

**Rx only CII**

This information for patients or their parents or caregivers is about TRADENAME, a medication intended for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Please read this before you start taking TRADENAME. It is not intended to replace your doctor's instructions or advice. If you have any questions about this material or about TRADENAME, be sure to talk to your doctor or pharmacist.

### **What is TRADENAME?**

TRADENAME is a central nervous system stimulant for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Dexmethylphenidate hydrochloride, the active ingredient of TRADENAME, is also found in methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 30 years. TRADENAME is available in a D-shaped tablet form, 2.5 mg, 5 mg, and 10 mg, and is intended to be used in doses of 5 to 20 mg per day, given as divided doses, as directed by your doctor.

### **What is Attention Deficit Hyperactivity Disorder (ADHD)?**

Attention Deficit Hyperactivity Disorder (ADHD) is a disorder characterized by symptoms of inattentiveness and/or hyperactivity-impulsivity inappropriate to the patient's age which interfere with functioning in two or more settings (*e.g.*, school and home). Symptoms of inattention may include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity-impulsiveness may 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 both types of symptoms. Symptoms must be present for at least 6 months to be certain of the diagnosis.

### **How Does TRADENAME Work?**

TRADENAME (dexmethylphenidate hydrochloride) is rapidly absorbed into the bloodstream and acts for a period of several hours. TRADENAME helps to increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

## **Before TRADENAME Treatment**

It is very important that ADHD be accurately diagnosed and that the need for medication be carefully assessed. It is important to remember that tradename is only part of the overall management of ADHD. Parents, teachers, physicians and other professionals are part of a team that must work together.

Before tradename treatment, your doctor should be made aware of any current or past physical or mental problems. Tell your doctor if there is a history of drug or alcohol abuse, depression, psychosis, epilepsy or seizure disorders, high blood pressure, glaucoma, facial tics (involuntary movements), or a family history of Tourette's syndrome.

Both your doctor and your pharmacist should also be informed of all medicines that you are taking, even if these drugs are not taken on a regular basis and are available without prescription. Your doctor will decide whether you can take Tradename with other medicines. Methylphenidate is known to interact with a number of other drugs. These include medicines to treat depression, such as monoamine oxidase inhibitors; to control seizures; and to thin blood. Sometimes these interactions may require a change in dosage, or occasionally stopping one of the drugs involved.

Tell your doctor if you are pregnant or nursing a baby.

## **Who Should Not Take TRADENAME?**

You should NOT take TRADENAME if:

- You have significant anxiety, tension, or agitation since TRADENAME may make these conditions worse.
- You are allergic to methylphenidate or any of the other ingredients in TRADENAME .
- You have glaucoma, an eye disease.
- You have tics or Tourette's Syndrome, or a family history of Tourette's Syndrome
- You are taking a monoamine oxidase inhibitor, a type of drug, or have discontinued a monoamine oxidase inhibitor in the last 14 days.

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

## **How Should I Take TRADENAME?**

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 TRADENAME?**

In the clinical studies with patients using TRADENAME, the most common side effects were stomach pain, fever, decreased appetite, and nausea. Other side effects seen with TRADENAME, include vomiting, dizziness, sleeplessness, 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 TRADENAME?**

Talk to your doctor *before* taking TRADENAME 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 an abnormal heart rate or rhythm

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

## **Can I Take TRADENAME with Other Medicines?**

Tell your doctor about *all* medicines that you are taking. Your doctor should decide whether you can take TRADENAME 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 TRADENAME with monoamine oxidase (MAO) inhibitors.

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

TRADENAME 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 TRADENAME .

## **Other Important Safety Information**

Abuse of TRADENAME 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 TRADENAME, tell your doctor if you are pregnant or plan on becoming pregnant. If you take TRADENAME, 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 TRADENAME .

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 TRADENAME treatment.

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

### **What Else Should I Know about TRADENAME?**

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

TRADENAME 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 TRADENAME with anyone else and take only the number of TRADENAME tablets prescribed by your doctor.

TRADENAME may be taken at the same time as food or with no food. TRADENAME 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 the container of TRADENAME in a safe place, away from high-traffic areas where other people could have accidental or unauthorized access to the medication. Keep track of the number of tablets so that you will know if any are missing. Sadly, someone who has easy access to TRADENAME may be able to give the tablets to others or misuse the medication.

### **Keep Out of the Reach of Children**

File: NDA/RitalinLA/21278Apltrwlabel.doc



NDA 21-278

Celgene Corporation  
Attention: Steve Thomas, Ph.D.  
Vice Pres., Regulatory Affairs and Project Mgmt.  
7 Powder Horn Drive  
Warren, New Jersey 07059

Dear Dr. Thomas

Please refer to your new drug application (NDA) dated October 25, 2000, received October 25, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for **TRADENAME** (dexmethylphenidate HCl) 2.5 mg, 5 mg, and 10 mg Tablets.

We acknowledge receipt of your submissions dated:

November 22, 2000	December 4, 2000	December 5, 2000
December 28, 2000	December 29, 2000	January 12, 2001
January 30, 2001	February 13, 2001	February 14, 2001
February 20, 2001	March 8, 2001	March 15, 2001
April 9, 2001	April 25, 2001	May 7, 2001
May 18, 2001	May 21, 2001	June 15, 2001
June 19, 2001	June 20, 2001	June 21, 2001
June 25, 2001	July 3, 2001	July 10, 2001
July 12, 2001		

This new drug application provides for the use of **TRADENAME** for the treatment of attention deficit disorder.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

### **Labeling Issues**

1. FDA's Office of Post-Marketing Drug Risk Assessment has evaluated your proposed proprietary trade name, i.e., Ritadex™, and has recommended that we not accept this trade name. The primary concern is confusion with the marketed methylphenidate product Ritalin®. There is a substantial potential for name confusion, with resultant medication errors. A patient for whom Ritalin® was intended but who received Ritadex™ would get twice the recommended dose of active enantiomer. A patient for whom Ritadex™ was intended, but who received Ritalin®, would get half the recommended dose of active enantiomer. Thus, we ask that you propose an alternative name.
2. Accompanying this letter as an attachment, is our labeling proposal, including explanations, for TRADENAME. We ask that you adopt this labeling for approval. If you would like to further discuss this labeling proposal, a teleconference may be arranged through the division project manager.

### **Worldwide Literature Update**

Please provide any new information on the worldwide regulatory status of TRADENAME, including the status of all actions either taken or pending before any foreign regulatory authorities.

### **Chemistry Issues**

#### **Drug Substance:**

1. Refer to page 1070 in the May 7, 2001 (BC) Amendment. For the Fisher Scientific LDPE bags, please provide the safety information which states that each of the bag's components meets the corresponding 21 CFR.
2. Refer to page 1255 in Volume 1.7. Please revise the following such that Johnson Matthey is depicted as the only drug substance supplier:
  - a) Stability Protocol for the First Three Full Scale Production Lots of d-MPH.
  - b) Proposed Half Matrix for Long Term Stability Trials, First Three Full Scale Production Lots of d-MPH.
3. Refer to page 1256 in Volume 1.7. Please revise the stability protocol annual commitment to include a 3 and 9 month time point as discussed in the ICH Q1A(R) document.
4. Refer to the revised regulatory specifications for dexmethylphenidate hydrochloride on page 3049 in the June 16, 2001 amendment. Based on the three Johnson Matthey commercial/validation lots, Certificates of Analyses submitted in the 5/21/01 amendment and based on the Johnson Matthey primary stability data submitted in the 5/21/01 amendment, we propose the specification limits be reduced to the following: R13 to NMT 0.30%; R15 to NMT 0.50%; and Total Impurities to NMT 1.20%.

5. Refer to pages 2347 – 2352 in the 5/21/01 (BC) Amendment and page 1727 in Volume 1.8. Please explain why Johnson Matthey has the impurities RI4 and RI2 depicted as hydrochloride salts and Celgene does not.
6. DMF 15059 was found to be inadequate on August 1, 2001.
7. Please note that the drug substance retest date is 12 months and can be extended based on the submission of real time stability data.

**Drug Product:**

1. During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by representatives of the FDA Office of Compliance. Satisfactory inspections will be required before this application may be approved.
2. Please provide the acceptance criteria for the Attribute Thickness in Table 7, In-process Specification for Drug Product Tablets (refer to page 95 in Volume 1.3, page 628 in the 3/8/01 (BC) Amendment, and page 668 in the 3/15/01 (BC) Amendment ). The footnote states that an acceptance criterion for this attribute will be set based on data gathered during drug product process scale up and validation; once set, the acceptance criterion will be amended to the NDA. However, we have not received the amendment.
3. Please refer to the revised regulatory specifications for Dexmethylphenidate HCl Tablets on page 3050 in the 6/16/01 amendment. Based on both the Mikart Certificate of Analyses submitted in the 6/21/01 and 7/12/01 amendments, and the Watson products' stability data at 25°C/60%RH (18 months) and 30°C/60%RH(12 months) submitted in the May 21, 2001 amendment, we propose the specification limits for RI3, RI5, and Total Impurities be reduced to the following: RI3 to NMT 2.50%, RI5 to NMT 0.75%, Total Impurities to NMT 3.65%.
4. Please note that the drug product expiration date is 24 months.
5. Please provide carton container drafts for the 2.5mg, 5.0mg , and the 10.0mg tablets.

**Clinical Pharmacology and Biopharmaceutics**

Please revise the *in vitro* dissolution specifications to Q = 75% in 30 minutes, which also leads to a change in sampling time to 30 minutes.

**Safety Update**

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

#### **Phase 4 Commitment**

Please commit to performing a study in juvenile rats in order to examine the effects of d-methylphenidate on developing systems, with particular emphasis on neurobehavioral and reproductive parameters. A proposed protocol for such a study should be submitted for our review.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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