PRODUCT MONOGRAPH

[C]Attenade™

(Dexmethylphenidate hydrochloride tablets)

2.5 mg, 5 mg and 10 mg tablets

Central Nervous System Stimulant

DATE OF PREPARATION:
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Control#:097675

PRODUCT MONOGRAPH

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(Dexmethylphenidate hydrochloride tablets)
2.5 mg, 5 mg and 10 mg tablets

THERAPEUTIC CLASSIFICATION

Central Nervous System Stimulant

ACTION AND CLINICAL PHARMACOLOGY

Attenade™ is the *d-threo*-enantiomer of methylphenidate hydrochloride. Methylphenidate hydrochloride is a 50/50 mixture of *d-threo*- and *l-threo*-enantiomers (racemic methylphenidate).

Pharmacodynamics

Attenade™ *(*dexmethylphenidate hydrochloride) is a central nervous system stimulant. Dexmethylphenidate, the more pharmacologically active enantiomer of the *d*- and *l*-enantiomers, is thought to block the reuptake of dopamine and norepinephrine into the presynaptic neuron and to increase the release of these monoamines into the extraneuronal space. The mode of therapeutic action in Attention-Deficit/Hyperactivity Disorder (ADHD) is not completely understood.

Pharmacokinetics

Absorption

Dexmethylphenidate hydrochloride is readily absorbed following oral administration of Attenade™. In patients with ADHD, plasma dexmethylphenidate concentrations reach a maximum in the fasted state, at about 1 to 1½ hours post-dose. The C_{max} was 21.4±6.5 after a 10 mg single dosing, as compared with 25.1±10.1 after 6 ½ days of repeated twice daily (bid) dosing. No differences in other pharmacokinetic parameters of dexmethylphenidate were noted following single and repeated bid dosing, indicating no significant drug accumulation in children with ADHD.

The mean pharmacokinetic parameter values in 9 children (average age 10 ± 2.4 years, range 7 - 15), with ADHD, following a single 10 mg dose and multiple dosing with 10 mg twice daily (bid) for 6½ days are summarized in Table 1.

Table 1

Dexmethylphenidate Pharmacokinetic Parameter Values in 9 Children with ADHD (Mean ± Standard Deviation)

	Single 10-mg Dose	Multiple 10 mg bid × 6½ days
C_{max} (ng/mL)	21.4±6.5	25.1±10.1*
T_{max} (h)	1.1±0.4	1.2±0.4
AUC (ng●h/mL)	82.4±20.6	90.4±24.2
$t_{½}$ (h)	2.3±0.4	2.2±0.4

* $p < 0.05$.

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

Food Effects

Food delays T_{max} of methylphenidate, but C_{max} and $AUC_{0\text{-inf}}$ are not affected. In a single dose study conducted in adults, coadministration of 2 x 10 mg Attenade™ with a high fat breakfast resulted in a dexmethylphenidate T_{max} of 2.9 hours post-dose as compared to a T_{max} of 1.5 hours post-dose when given in a fasting state. C_{max} and $AUC_{0\text{-inf}}$ were comparable in both the fasted and non-fasted states.

Distribution

Plasma dexmethylphenidate concentrations in children decline exponentially following oral administration of Attenade™. The mean plasma elimination half-life is approximately 2.2 hours. Protein binding has not been determined for dexmethylphenidate, however, in humans 15± 5% of methylphenidate is bound to plasma proteins.

Metabolism and Elimination

In humans, dexmethylphenidate is metabolized primarily to *d*-α-phenyl-piperidine acetic acid (also known as *d*-ritalinic acid) by de-esterification. The de-eserification is enantiospecific. This metabolite has little pharmacologic 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.

Attenade™ is believed to have a pattern of elimination similar to methylphenidate. 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. (See **Special Populations, Renal Insufficiency.**)

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 dexmethylphenidate $AUC_{0\text{-}inf}$ values (adjusted for body weight) following single 2 x 10 mg doses of Attenade™ were 25%-35% higher in adult female volunteers (n=6) compared to male volunteers (n=9). Both t_{max} and $t_{1/2}$ were comparable for males and females.

Age
The pharmacokinetics of dexmethylphenidate after Attenade™ administration has not been studied in children less than 6 years of age. When single doses of Attenade™ were given to children between the ages of 6 to 12 years and healthy adult volunteers, C_{max} of dexmethylphenidate was similar, however, children showed somewhat lower AUCs compared to adults.

Renal Insufficiency

There is no experience with the use of Attenade™ in patients with renal insufficiency. There is very limited experience with the use of methylphenidate in patients with renal insufficiency. Renal clearance is not significant for methylphenidate elimination, but the main methylphenidate product, PPA, is predominantly (80%) cleared through the urine.

Hepatic Insufficiency
There is no experience with the use of methylphenidate in patients with hepatic insufficiency. (For Drug Interactions, see PRECAUTIONS.)

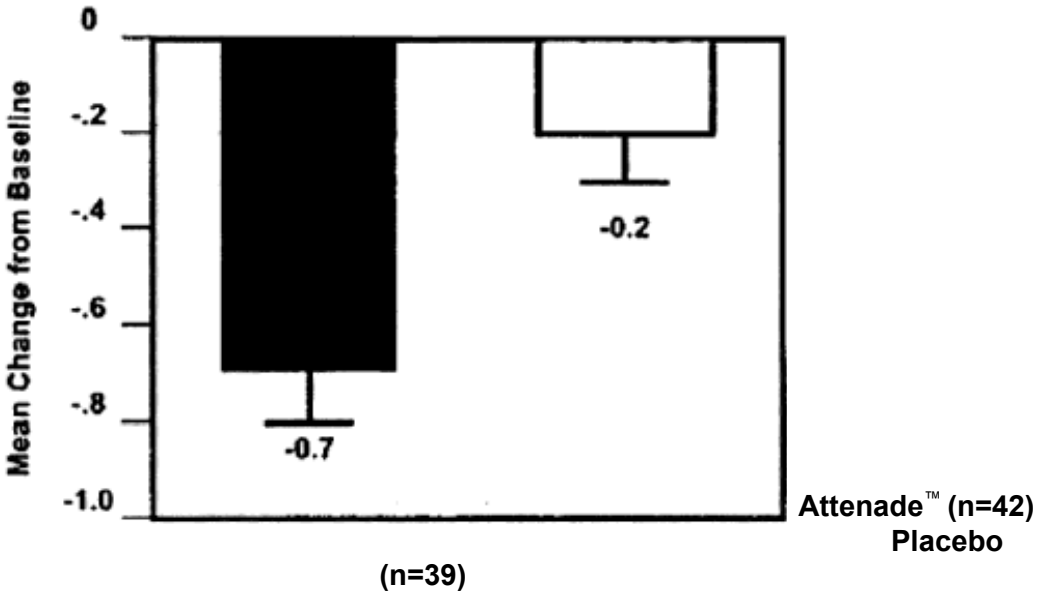
Clinical Studies

Attenade™ 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 Attenade™ versus placebo.

Attenade™ (5, 10, or 20 mg/day total dose), racemic methylphenidate (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, 3.2 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 Attenade™ showed a statistically significant improvement in symptom scores

from baseline over patients who received placebo.

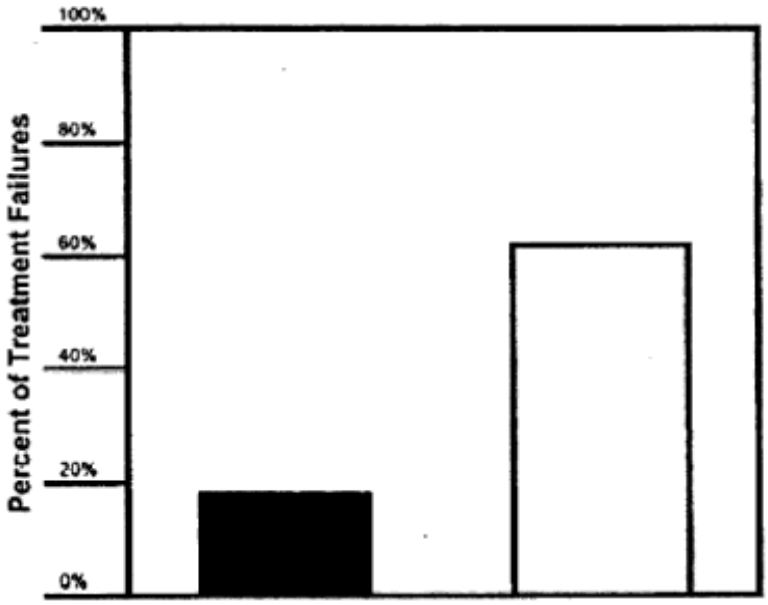
Figure 1
Mean Change from Baseline in Teacher SNAP-ADHD Scores
in a 4-week Double-blind Placebo-controlled Study of Attenade™



Note: 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 Attenade™ 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 Attenade™



INDICATIONS AND CLINICAL USE

Attenade™ is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD), in children 6-17 years of age.

The efficacy of Attenade™ 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 be persistent, must be more severe than is typically observed in individuals at a comparable level of development, 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. For a Combined Type diagnosis,

both inattentive and hyperactive-impulsive criteria must 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 patient and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program
Attenade™ 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. Drug treatment is 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 in children and adolescents with this diagnosis 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 Attenade™ for long-term use, ie for more than 4 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use Attenade™ for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, patients known to be hypersensitive to methylphenidate or other components of the product.

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

Glaucoma
Attenade™ is contraindicated in patients with glaucoma.

Motor and Verbal Tics
Attenade™ is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see **ADVERSE REACTIONS**).

Monoamine Oxidase Inhibitors
Attenade™ 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

Sudden Death and Pre-existing Structural Cardiac Abnormalities:

Sudden death has been reported in association with stimulant drugs used for ADHD treatment at usual doses in children with structural cardiac abnormalities. Attenade™ generally should not be used in children, adolescents, or adults with known structural cardiac abnormalities.

General
Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: a) are involved in strenuous exercise or activities, b) use ADHD drugs or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment, a personal and family history should be obtained. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered.

Depression
Attenade™ should not be used to treat severe depression.

Fatigue
Attenade™ 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 Attenade™ in children, is 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.

Psychotic Disorders
Clinical experience suggests that administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder in psychotic children.

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, or suspected seizures, the drug should be discontinued.

Hypertension and Other Cardiovascular Conditions

Attenade should be used cautiously in patients with mild hypertension and other cardiovascular conditions. Blood pressure should be monitored at appropriate intervals in all patients taking Attenade™, especially in patients with hypertension. In the placebo controlled studies, the mean pulse increase was 2-5 bpm for both Attenade™ 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.

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

Drug Abuse and Dependence
Attenade™ 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.

PRECAUTIONS

Laboratory Monitoring
Periodic laboratory tests are advised during prolonged therapy. The tests should included but be not limited to, hematologic parameters, including complete blood count, differential and platelet counts, and liver enzymes.

Information for Patients
Patient information is printed at the end of this document. To assure safe and effective use of Attenade™, the information and instructions provided in the patient information section should be discussed with patients.

Occupational Hazards
Any psychoactive drug may impair judgement, thinking or motor skills. Therefore patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect their performance adversely.

Drug Interactions

Because of possible effects on blood pressure, Attenade should be used cautiously with pressor agents.

Monoamine oxidase inhibitors
Methylphenidate 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). The same Contraindication applies to Attenade. See CONTRAINDICATIONS)

Inhibition of Drug Metabolism by methylphenidate
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 dexmethylphenidate.

Clonidine
Serious adverse events have been reported in concomitant racemic methylphenidate 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.

Alcohol
Alcohol may exacerbate the CNS adverse effect of psychoactive drugs. Therefore, patients undergoing Attenade™ therapy should be advised to avoid alcohol during treatment.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Lifetime carcinogenicity studies have not been carried out with dexmethylphenidate. 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 relativity 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+/-, 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 60-74 mg/kg/day of racemic methylphenidate.

D-thero-methylphenidate 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 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: Teratogenic Effects

Pregnancy Category C: In studies conducted in rats and rabbits, dexmethylphenidate 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 dexmethylphenidate 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 dexmethylphenidate 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. Attenade™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether dexmethylphenidate is excreted in human milk. Because many drugs are excreted in human milk, Attenade™ should not be administered to a nursing woman unless the anticipated benefits to the mother outweigh the potential hazards to the infant.

Pediatric Use

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

Renal Insufficiency
There is only very limited experience of methylphenidate use in patients with renal insufficiency. (See **PHARMACOKINETCS**, Metabolism and Excretion, **Special Populations,** Renal Insufficiency)

Hepatic Insufficiency
There is no experience of methylphenidate use in patients with hepatic insufficiency. (See **PHARMACOKINETCS**, Metabolism and Excretion, **Special Populations,** Hepatic Insufficiency)

ADVERSE REACTIONS

The pre-marketing development program for Attenade™ included exposures in a total of 696 participants in clinical trials (684 patients, 12 healthy adult subjects). These participants received Attenade™ 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 Attenade™

Adverse Events Associated with Discontinuation of Treatment
No Attenade-treatment patients discontinued treatment due to adverse events in 2 placebo-controlled trails. In open and placebo controlled trials, 50 of 684 children treated with Attenade™ (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 in 2 or More Attenade™-Treated Patients
Table 1 enumerates treatment-emergent adverse events for a double-blind placebo-controlled,

parallel group trial in children with ADHD at Attenade™ doses of 5, 10, and 20 mg/day. The table includes only those events that occurred in 2 or more of patients treated with Attenade™ bid, or placebo bid. 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 Events[1] in a 4-Week Placebo-Controlled Clinical Trial of Attenade

Body Systems	**Preferred Term**	**Attenade™, bid** (n = 44)	**Placebo** (n = 42)
General	Abdominal pain	21	12
	Headache	16	10
	Fever	9	2
	Pain	7	2
Digestive	Nausea	11	2
	Anorexia	9	0
	Vomiting	7	5
	Diarrhea	5	2
Metabolic	Ketosis	5	0
Nervous	Emotional lability	7	2
	Somnolence	7	2
	Insomnia	5	2
	Nervousness	5	2
	Personality	2	5
Respiratory	Rhinitis	16	10
	Epistaxis	7	0
	Pharyngitis	5	2

[1] Treatment-emergent adverse events, regardless of causality, occurring in 2 or more Attenade™ or placebo treated patients. Incidence has been rounded to the nearest whole number.

Postmarket reports
Adverse events reported since market introduction of patients taking Attenade include tics, skin rash, agression, tachycardia. Sudden cardiac death has been reported in association with stimulant drugs used for ADHD treatment.

Adverse Events with racemic Methylphenidate Products
Nervousness and insomnia are the most common adverse reactions reported with other racemic 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

Hepatobiliary: 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.

OVERDOSAGE AND TREATMENT

Signs and Symptoms
Signs and symptoms of acute methylphenidate overdosage, 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. Alcohol may induce the production of ethylphenidate during Attenade™ therapy, and the amount of ethylphenidate produced is proportional to the concentration of blood alcohol. The toxicity of ethylphenidate has not been established.

Efficacy of peritoneal dialysis for Attenade™ overdosage has not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
ATTENADE should be administered starting at the lowest possible dose. Dosage should then be individually and slowly adjusted, to the lowest effective dosage, since individual patient response to ATTENADE varies widely.

ATTENADE should not be used in patients with symptomatic cardiovascular disease and should generally not be used in patients with known structural cardiac abnormalities (See CONTRAINDICATIONS and WARNINGS).

Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: a) are involved in strenuous exercise or activities, b) use ADHD drugs or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment, a personal and family history should be obtained. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered.

Patients who are considered to need extended treatment with ATTENADE should undergo periodic evaluation of their cardiovascular status. (see WARNIGS)

Caution should be exercised in prescribing concomitant drugs.

For children 6-17 years of age: Attenade™ is administered twice daily, at least 4 hours apart. Attenade™ may be administered with or without food.

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

Dosage recommendations

Patients New to Methylphenidate
The recommended starting dose of Attenade™ for patients who are not currently taking 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, they should stop taking methylphenidate and commence taking the recommended starting dose of Attenade™ which is half the existing dose of racemic methylphenidate, (eg. a patient receiving 10 mg racemic methylphenidate would be started on 5 mg Attenade™). The maximum recommended Attenade™ dose is 20 mg/day (10 mg twice daily).

Methylphenidate and dexmethylphenidate should not be used at the same time.

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

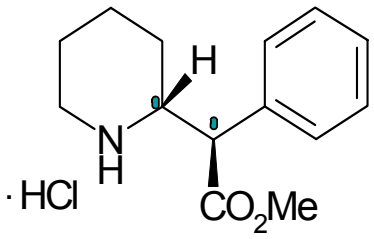
If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued.

PHARMACEUTICAL INFORMATION

Proper Name: dexmethylphenidate HCl

Chemical Name: (R,R')-(+)-α-phenyl-2-piperidineacetic acid, methyl ester, hydrochloride

Structural Formula:



Note: = asymmetric carbon centers

Molecular formula: $C_{14}H_{19}NO_2 \cdot HCl$

Molecular weight: 269.77

Characteristics: 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.

Formulation: The tablets also contain: Lactose monohydrate, pregelatinized starch, sodium starch glycolate, microcrystalline cellulose, magnesium stearate. The 2.5 mg tablet contains FD&C blue no.1 #5516 aluminum lake and the 5 mg tablet contains D & C yellow lake #10.

STABILITY AND STORAGE RECOMMENDATIONS

Store Attenade™ tablets between 15-30 ºC. Protect from light and moisture. Keep out of reach of children.

AVAILABILITY OF DOSAGE FORMS

Attenade™ Tablets 2.5 mg: Each pale blue, D-shaped tablet, embossed with "D" on upper convex face and dosage strength on lower convex face, contains 2.5 mg of dexmethylphenidate HCl. Available in bottles of 100.

Attenade™ Tablets 5 mg: Each yellow, D-shaped tablet, embossed with "D" on upper convex face and dosage strength on lower convex face, contains 5 mg of dexmethylphenidate HCl. Available in bottles of 100.

Attenade™ Tablets 10 mg: Each white, D-shaped tablet, embossed with "D" on upper convex face and dosage strength on lower convex face, contains 10 mg of dexmethylphenidate HCl. Available in bottles of 100.

INFORMATION FOR PATIENTS/PARENTS

Attenade™
Dexmethylphenidate tablets

This information for patients or their parents or caregivers is about Attenade™, a medication intended for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6-17. It is very important that ADHD be accurately diagnosed and that the need for medication be carefully assessed. It is important to remember that Attenade™ is only part of the overall management of ADHD. Parents, teachers, physicians and other professionals are part of a team that must work together.

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

What is Attenade™?
Attenade™ is a central nervous system stimulant for the treatment of ADHD. Dexmethylphenidate hydrochloride, the active ingredient of Attenade™, is part of methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 30 years. This condition can be found in adults and/or children and teenagers.

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.

What does Attenade™ Do ?
Attenade™ is readily absorbed into the bloodstream and acts for a period of several hours. Attenade™ helps to increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Who Should Not Take Attenade™?
Attenade™ should not be taken if you / your child have:
- symptomatic cardiovascular disease (a heart condition)
- moderate to severe high blood pressure
- arteriosclerosis (hardened arteries)
- hyperthyroidism (an overactive thyroid gland)
- You are taking monoamine oxidase inhibitors (a type of drug, see Interactions with this Medication).
- significant anxiety, tension, or agitation because Attenade™ may make these conditions worse;
- are allergic to methylphenidate or any of the other ingredients in Attenade™;

- glaucoma, an eye disease;
- or a family history of motion tics (hard-to-control, repeated twitching of any parts of your body), verbal tics (hard-to-control repeating of sounds or words), or Tourette's syndrome.

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

What does Attenade™ Contain ?
Attenade™ tablets contain:
Medicinal ingredient: dexmethylphenidate hydrochloride
Non-medicinal ingredients: lactose monohydrate, pregelatinized starch, sodium starch glycolate, microcrystalline cellulose, magnesium stearate. The 2.5 mg tablets also contain FD&C blue no. 1 aluminum lake and the 5 mg tablets contain D&C yellow lake no. 10.

Attenade™ 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 Must I Discuss with my Doctor before Taking Attenade™?
Abuse of Attenade™ 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.

Sudden death has been reported in association with stimulant drugs for ADHD treatment in children with structural heart abnormalities. Attenade generally should not be used in patients with known structural heart abnormalities.

Talk to your doctor before taking Attenade™ if:

- You are being treated for depression or have symptoms of depression such as feelings of sadness, worthlessness, and hopelessness.
- You have motion tics or verbal tics.
- You have someone in your family with motion tics, verbal tics, or Tourette's syndrome.
- You have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis.
- You have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms).
- You have mild high blood pressure.
- You have an abnormal heart rate or rhythm.
- Have structural heart abnormalities
- Have a family history of sudden death or death related to heart problems
- Do strenuous exercise
- Take other stimulant drugs

Before Attenade™ 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 the patient

is taking, even if these drugs are not taken on a regular basis and are available without prescription.

Before taking Attenade™, tell your doctor if you are pregnant or plan on becoming pregnant.

If you take Attenade™, it may be in your breast milk. Tell your doctor if you are nursing a baby.

Attenade may affect your ability to drive.

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

Your doctor will monitor your progress with Attenade and may require you to do occasional tests to ensure your health and safety.

Can Attenade™ be taken with Other Medicines?
Attenade™ should not be taken with monoamine oxidase (MAO) inhibitors, as it may result in severe high blood pressure.

Tell your doctor about all medicines that are being taken. Your doctor should decide Attenade™ can be taken with other medicines. These include:

- Other medicines that a doctor has prescribed.
- Medicines that you can buy without a prescription.
- Any herbal remedies.
- Clonidine
- Alcohol

Before Attenade™ Treatment:
Your doctor will decide whether you can take Attenade™ 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, tricyclic antidepressants, or selective serotonin reuptake inhibitors (SSRIs); to control seizures; and to thin blood. Sometimes these interactions may require a change in dosage, or occasionally stopping one of the drugs involved.

Do not start taking a new medicine or herbal remedy before checking with your doctor.

When and How Should Attenade™ tablets be taken?
Dosage: For children 6-17 years of age - The tablets should be taken twice daily with or without food, once in the morning and once at mid-day at least 4 hours apart. Attenade™ has not been studied in children under 6 years of age. Do not use alcohol when taking Attenade™.

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 the treatment to check the symptoms while you are not taking the drug.

Your doctor may assess the effect of your treatment and dosage periodically to determine whether longer term use will be beneficial. Also, if no improvement is seen after one month, your doctor may direct you to stop taking Attenade™.

Overdose: Call your doctor **immediately** if you take more than the amount of Attenade™ prescribed by your doctor.

What are the Possible Side Effects of Attenade™ ?
In the clinical studies with patients using Attenade™, the most common side effects were stomach pain, headache, fever, decreased appetite, and nausea. Other side effects seen with Attenade™ 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 any side effects develop, talk to your doctor.

Tell your doctor if you have blurred vision when taking Attenade™.

Other Important Safety Information:
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 Attenade™ treatment.

What Else Should I Know about Attenade™?
Attenade™ 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 Attenade™ with anyone else and take only the number of Attenade™ tablets prescribed by your doctor.

Attenade™ should be stored in a safe place at room temperature (between 15 - 30 ^{o}C). Do not store this medicine in hot, damp, or humid places. Protect from light.

Special Information for Parents, Caregivers or Patients
Keep the container of Attenade™ in a safe place, away from high-traffic areas where other people could have accidental or unauthorized access to the medication and to avoid diversion of this product for nonmedical use. Keep track of the number of tablets so that you will know if any are missing. Someone who has easy access to Attenade™ may be able to give the tablets to others or misuse the medication.

Keep Out of the Reach of Children

Biovail Pharmaceuticals Canada
7150 Mississauga Rd.
Mississauga, Ontario
L5N 8M5

1-866-825-8120

PHARMACOLOGY

The plasma half-life of dexmethylphenidate following oral dosing with either *d*- or *d,l*-MPH is between 1 to 2 hours in all species examined (rats, rabbits, and dogs). Plasma half-lives for the metabolites *l*- and/or *d*-ritalinic acid (RA) were consistently longer than for the parent compounds (*l*- and/or dexmethylphenidate) following oral administration. Half-lives ranged from 1 to 3 hours in rats and 4 to 8 hours in rabbits and dogs and had a tendency to increase with longer exposure times.

In mice, rats and dogs approximately 60 to 80% of an orally administered dose of [^{14}C]-methylphenidate was recovered in the urine, with the remainder in feces. Following i.p. or oral administration of [^{14}C]-methylphenidate to mice or rats, 50 to 60 and 30 to 40% of the administered radioactivity was recovered within 48 hours in urine and feces, respectively. In dogs, 70% of orally administered [^{14}C]-methylphenidate was recovered in urine within 5 hours.

An *in vitro* metabolism study examining the effect of *d*-, *l*-, or *d,l*-MPH on the activity of various cytochrome P450 (CYP) isoforms demonstrated only slight inhibition (25 to 30%) of the activity of CYP2D6 by *d*-, *l*-, or *d,l*-MPH. This inhibition was not considered to be of clinical significance.

TOXICOLOGY

The maximum tolerated dose (MTD) in rats for *d*- and *d,l*-MPH was estimated to be 100 and 200 mg/kg/day (given as 50 and 100 mg/kg b.i.d.), respectively. Clinical signs following administration of *d*- or *d,l*-MPH were hyperactivity, hypersensitivity, and self mutilation.The MTD in dogs for *d*- and *d,l*-MPH, was estimated to be 10 and 20 mg/kg/day (given as 5 and 10 mg/b.i.d.), respectively. Clinical signs following administration of *d*- or *d,l*-MPH in dogs were hyperactivity, salivation, and increased body temperature.

In repeat dose toxicity studies the maximum dose levels of *d*- and *d,l*-MPH that could be used were limited by the effects of CNS overstimulation. Repeat dose studies in rats and dogs were conducted for durations of 2 weeks and 2 months. In general, there were no effects seen following dosing with dexmethylphenidate that were not also observed following dosing with *d,l*-MPH that provided an equimolar amount of dexmethylphenidate . The No-Observed Effect-Level (NOAEL) for dexmethylphenidate was less than 20 mg/kg/day in rats and 1 mg/kg/day in dogs. For *d,l*-MPH, the NOAEL was less than 40 mg/kg/day in rats and 2 mg/kg/day in dogs. Higher doses of *d*- or *d,l*-MPH resulted in signs of hyperactivity, hypersensitivity and self-mutilation in rats, and in hyperactivity and salivation in dogs. Changes in hematological parameters were observed following 14 days of dosing of either *d*- or *d,l*-MPH in rats but not after 90 days of dosing. Changes included decreases in mean platelets and increases in mean activated partial thrombin time in males and increases in mean eosinophils in females. The only consistent changes noted in dogs following repeat administration of either *d*- or *d,l*-MPH included weight loss in both males and females.

The reproductive toxicity of dexmethylphenidate was studied, along with that of *d,l*-MPH, in modified Segment II studies in rats and rabbits that incorporated a natural delivery and postnatal observation phase. Clinical signs observed in rats following dosing with either *d*- or *d,l*-MPH were indicative of psychostimulation, such as repetitive sniffing and pawing,

hyperreactivity, hyperactivity, dilated pupils, excess salivation, and aggressive behavior. The number of rats with repetitive pawing and aggression was significantly lower with 20 mg/kg/day of dexmethylphenidate compared to 40 mg/kg/day of *d,l*-MPH. The maternal no-observable-adverse-effect level (NOAEL) of dexmethylphenidate is 2 mg/kg/day. Six (6) and 20 mg/kg/day of dexmethylphenidate and 40 mg/kg/day of *d,l*-MPH resulted in significant increases in the incidence of adverse clinical observations including decreased maternal body weight and body weight gain, altered food consumption, and increased duration in gestation. Greater incidences of adverse effects and reductions in gestation, body weight gain, and food consumption occurred with *d,l*-MPH compared to dexmethylphenidate. No developmental effects were observed at maternal doses of up to 20 mg/kg/day of dexmethylphenidate or 40 mg/kg/day of *d,l*-MPH. In rabbits, the NOAEL for maternal toxicity was 20 mg/kg/day of dexmethylphenidate. Adverse clinical observations (repetitive sniffing, chewing, head bobbing, and hyperactivity) were evident at 100 mg/kg/day of dexmethylphenidate. Clinical observations were similar in nature between *d*- and *d,l*-MPH. However, the incidence and severity were generally greater in animals given *d,l*-MPH compared to animals given molar equivalent doses of dexmethylphenidate. There was no developmental toxicity with *d*- and *d,l*-MPH.

Lifetime carcinogenicity studies have not been carried out with dexmethylphenidate . In a lifetime carcinogenicity study carried out in B6C3F1 mice, racemic methylphenidate caused an increase in hepatocellular adenoma, 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 tumour 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. This dose is approximately 200 times and 15 times the maximum recommended human dose of dexmethylphenidate on a mg/kg and mg/m^2 basis, respectively. Taking into consideration systemic exposure in mice receiving comparable doses of dexmethylphenidate , these mice had mean plasma concentrations of dexmethylphenidate HCl that were comparable to the plasma concentration in humans after dosing with the maximum recommended human daily dose.

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 50 mg/kg/day. This dose is approximately 150 times and 20 times the maximum recommended human dose of dexmethylphenidate on a mg/kg and mg/m^2 basis, respectively. A subsequent pharmacokinetic study has estimated that these rats had mean plasma dexmethylphenidate HCl concentrations that were approximately 10-fold higher than those of humans, after dosing with the maximum recommended human daily dose.

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

Dexmethylphenidate 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 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.

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