

**PRODUCT MONOGRAPH**

**APO-METHYLPHENIDATE**

**Methylphenidate Hydrochloride Tablets USP**

**10 mg and 20 mg tablets**

**APO-METHYLPHENIDATE SR**

**Methylphenidate Hydrochloride Extended Release Tablets USP**

**20 mg tablets**

**Central Nervous System Stimulant**

**APOTEX INC.  
150 Signet Drive  
Weston, Ontario  
M9L 1T9**

***Control #093145***

**DATE OF PREPARATION:  
March 31, 2005  
DATE OF REVISION:**

**PRODUCT MONOGRAPH**

APO-METHYLPHENIDATE  
Methylphenidate Hydrochloride Tablets USP  
10 and 20 mg

APO-METHYLPHENIDATE SR  
Methylphenidate Hydrochloride Extended Release Tablets USP  
20 mg

**THERAPEUTIC CLASSIFICATION**

Central Nervous System Stimulant

**ACTIONS AND CLINICAL PHARMACOLOGY**

Methylphenidate hydrochloride is a mild central nervous system stimulant with more prominent effects on mental than motor activities.

The mode of action in man is not completely understood, but its stimulant effects are thought to be due to cortical stimulation and possibly to stimulation of the reticular activating system.

There is neither specific evidence which clearly establishes the mechanism whereby methylphenidate produces its mental and behavioural effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

Methylphenidate hydrochloride is rapidly and extensively absorbed from the tablets following oral administration; however, owing to extensive first-pass metabolism, bioavailability is low (approx. 30%) and large individual differences exist (11-52%). In one study, the administration of methylphenidate hydrochloride with food accelerated absorption, but had no effect on the amount absorbed.

Peak plasma concentrations of 10.8 and 7.8 ng/mL were observed, on average, 2 hours after administration of 0.30 mg/kg in children and adults, respectively. Peak plasma concentrations showed marked variability between subjects. Both the area under the concentration-time curve (AUC), and the peak plasma concentrations ( $C_{max}$ ) showed dose-proportionality.

Methylphenidate is eliminated from the plasma with a mean half-life of 2.4 hours in children and 2.1 hours in adults. The apparent mean systemic clearance is 10.2 and 10.5 liters/hr/kg in children and adults, respectively for a 0.3 mg/kg dose. These data indicate that the pharmacokinetics of methylphenidate in hyperactive children is similar to that in healthy adult volunteers. The apparent distribution volume of methylphenidate in children was approximately 20 liters/kg, with substantial variability (11-33 liters/kg).

Following oral administration of methylphenidate, 78-97% of the dose is excreted in the urine and 1-3% in the feces in the form of metabolites within 48-96 hours. The main urinary metabolite is ritalinic acid ( $\alpha$ -phenyl-2-piperidine acetic acid, PPAA); unchanged methylphenidate is excreted in the urine in small quantities (<1%). Peak PPAA plasma concentrations occurred at approximately the same time as peak methylphenidate concentrations, however, levels were several-fold greater than those of the unchanged drug. The half-life of PPAA was approximately twice that of methylphenidate.

In blood, methylphenidate and its metabolites are distributed between plasma (57%) and erythrocytes (43%). Methylphenidate and its metabolites exhibit low plasma protein binding (approx. 15%).

Methylphenidate in the extended-release tablets is more slowly but as extensively absorbed as in the regular tablets. Relative bioavailability of the methylphenidate hydrochloride extended-release tablet, compared to the methylphenidate hydrochloride tablet, measured by the urinary excretion of the methylphenidate major metabolite (PPAA), was 105% (49-168%) in children and 101% (85%-152%) in adults. The time to peak rate in children was 4.7 hours (1.3-8.2 hours) for the extended-release tablets and 1.9 hours (0.3-4.4 hours) for the regular tablets. The elimination half-life and the cumulative urinary excretion of PPAA are not significantly different between the two dosage forms. An average of 67% of the extended-release tablet dose was excreted in children as compared to 86% in adults.

#### Comparative Bioavailability

Apo-Methylphenidate 20 mg tablets: A comparative bioavailability study was performed using healthy adult volunteers. The rate and extent of absorption of methylphenidate were measured and compared following administration of a 20 mg dose of either Apo-Methylphenidate 20 mg tablets or Ritalin 20 mg tablets under fasting conditions. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data Methylphenidate (Dose: 1 x 20 mg) From Measured Data			
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	Apo-Methylphenidate	Ritalin®†	
AUC <sub>T</sub> (pg•hr/mL)	47382 50648 (40)	46943 50275 (42)	100.9
AUC <sub>I</sub> (pg•hr/mL)	48383 51710 (40)	48026 51442 (42)	100.7
C <sub>max</sub> (pg/mL)	9246 9780 (35)	8786 9216 (33)	105.2
T <sub>max</sub> (hr)*	1.88 (42)	2.26 (35)	-
t <sub>1/2</sub> (hr)*	3.44 (23)	3.49 (23)	-
* Arithmetic means (CV%).			
** Based on the least squares estimate.			
† Ritalin® is manufactured by Novartis Pharmaceuticals Canada Inc., and was purchased in Canada.			

Apo-Methylphenidate SR 20 mg tablets: Comparative bioavailability studies were performed using healthy adult volunteers. The rate and extent of absorption of methylphenidate were measured and compared following administration of a 20 mg dose of either Apo-Methylphenidate SR 20 mg tablets or Ritalin® SR 20 mg tablets under fasting and fed conditions. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data Methylphenidate HCl Extended Release (Dose: 1 x 20 mg) From Measured Data Under Fasting Conditions - Based on Methylphenidate			
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	Apo-Methylphenidate SR	Ritalin® SR†	
AUC <sub>T</sub> (pg.hr/mL)	37369 39532 (34)	37064 39115 (34)	100.8
AUC <sub>I</sub> (pg.hr/mL)	39007 41000 (33)	38523 40503 (34)	101.3
C <sub>MAX</sub> (pg/mL)	4643 4848 (31)	4956 5185 (32)	93.7
T <sub>MAX</sub> <sup>*</sup> (hr)	4.86 (12)	4.47 (21)	
T <sub>1/2</sub> <sup>*</sup> (hr)	4.14 (17)	3.37 (22)	
* Arithmetic means (CV%).			
** Based on the least squares estimate.			
† Ritalin® SR is marketed by Novartis Pharmaceuticals Canada Inc. (Dorval, QC, Canada).			

Summary Table of the Comparative Bioavailability Data Methylphenidate HCl Extended Release (Dose: 1 x 20 mg) From Measured Data Under Fed Conditions - Based on Methylphenidate			
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	Apo-Methylphenidate SR	Ritalin® SR†	
AUC <sub>T</sub> (pg.hr/mL)	54979 62430 (74)	54486 61267 (68)	100.9
AUC <sub>I</sub> (pg.hr/mL)	56664 65167 (79)	55944 63221 (70)	101.3
C <sub>MAX</sub> (pg/mL)	7027 7692 (60)	7157 7946 (64)	98.2
T <sub>MAX</sub> <sup>*</sup> (hr)	3.72 (33)	3.70 (28)	
T <sub>1/2</sub> <sup>*</sup> (hr)	4.19 (22)	3.45 (24)	
* Arithmetic means (CV%).			
** Based on the least squares estimate.			
† Ritalin® SR is marketed by Novartis Pharmaceuticals Canada Inc. (Dorval, QC, Canada).			

## **INDICATIONS AND CLINICAL USE**

### **1. Attention-Deficit Hyperactivity Disorder (ADHD)**

Previously known as Attention-Deficit Disorder. Other terms being used to describe this behavioural syndrome include: Minimal Brain Dysfunction, Hyperkinetic Disorder, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction and Psycho-Organic Syndrome of Children.

APO-METHYLPHENIDATE (methylphenidate hydrochloride) is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioural syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity. The diagnosis should be made according to the DSM-IV criteria. Non-localizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

**Special Diagnostic Considerations:** Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Proper diagnosis requires medical and neuropsychological, educational and social investigation.

Characteristics commonly reported include: history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. 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 one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe stimulant medication must be based on rigorous assessment of the severity of the child's symptoms.

## 2. Narcolepsy

### **CONTRAINDICATIONS**

Anxiety, tension, agitation, thyrotoxicosis, tachyarrhythmias, severe angina pectoris and glaucoma. Known or suspected hypersensitivity to the drug or its excipients. Also contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

### **WARNINGS**

APO-METHYLPHENIDATE (methylphenidate hydrochloride) should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established.

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. In addition, the use of "Drug Holidays" is recommended, that is, withholding the drug on weekends and during school holidays inasmuch as the clinical situation permits.



APO-METHYLPHENIDATE should not be used to treat severe exogenous or endogenous depression. Clinical experience suggests that in psychotic children, administration of methylphenidate hydrochloride may exacerbate symptoms of behavioural disturbance and thought disorder.

APO-METHYLPHENIDATE should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that methylphenidate hydrochloride may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures and, very rarely, in patients with no prior EEG evidence nor history of seizures. Clinical experience has shown that a small number of patients may experience an increase in seizure frequency when treated with methylphenidate hydrochloride. If seizure frequency rises, the drug should be discontinued.

Blood pressure should be monitored at appropriate intervals in all patients taking APO-METHYLPHENIDATE, especially those with hypertension.

#### Usage In Pregnancy And Lactation

Experience to establish safe use of methylphenidate hydrochloride during pregnancy is limited. In rat studies, methylphenidate hydrochloride did not affect reproductive performance or fertility, and had no embryotoxic, fetotoxic or teratogenic effects at doses 2 to 5 times the human therapeutic dose, however the implications of these findings to human use is not clear.

Therefore, APO-METHYLPHENIDATE should not be given to pregnant women unless the potential benefit outweighs the risk to fetus. It is not known whether the active substance of APO-METHYLPHENIDATE and/or its metabolites pass into the breast milk. For safety reasons, the physician should assess the patient's medical condition and advise one of the following options: refrain from breast-feeding their infants while taking APO-METHYLPHENIDATE, or discontinue the drug while nursing.

**Drug Dependence:** APO-METHYLPHENIDATE should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychocological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic over activity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

Clinical data indicate that treatment with methylphenidate hydrochloride during childhood and/or adolescence does not seem to result in increased predisposition for addiction.

### **PRECAUTIONS**

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

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

Drug treatment is not indicated in all cases of Attention Deficit Hyperactivity Disorders and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe APO-METHYLPHENIDATE (methylphenidate hydrochloride) should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more abnormal behavioural characteristics. Where these symptoms are associated with acute stress reactions, treatment with APO-METHYLPHENIDATE is usually not indicated.

Long-term effects of APO-METHYLPHENIDATE in children have not been well established.

Because APO-METHYLPHENIDATE may affect performance, patients should be cautioned against engaging in hazardous activities (i.e., operation of automobiles or dangerous machinery).

#### Drug Interactions

APO-METHYLPHENIDATE may reduce the antihypertensive effect of guanethidine. Use cautiously in patients being treated with pressor agents and MAO inhibitors.

Human pharmacologic studies have shown that methylphenidate hydrochloride may inhibit the metabolism of coumarin anticoagulants, some anticonvulsants (e.g. phenobarbital, diphenylhydantoin, primidone), phenylbutazone and tricyclic antidepressants. Downward dosage adjustments of these drugs may be required when given concomitantly with APO-METHYLPHENIDATE.

Alcohol may exacerbate the adverse CNS effect of psychoactive drugs, including APO-METHYLPHENIDATE. Therefore, patients should be advised to abstain from alcohol during treatment.

### **ADVERSE REACTIONS**

Frequency estimate: very common  $\geq 10\%$ , common  $\geq 1\%$  to  $< 10\%$ ; uncommon  $\geq 0.1\%$  to  $< 1\%$ ; rare  $\geq 0.01\%$  to  $< 0.1\%$ ; very rare  $< 0.01\%$

Nervousness and insomnia are very common adverse reactions. They occur at the beginning of treatment, but can usually be controlled by reducing dosage and/or omitting the afternoon or evening dose. Decreased appetite is also common but usually transient.

#### **Central And Peripheral Nervous System**

**Common:** dizziness, drowsiness, headache, dyskinesia.

**Rare:** Symptoms of visual disturbances, difficulties in visual accommodation and blurred vision.

**Very rare:** hyperactivity, convulsions, muscle cramps, choreoathetoid movements, tics, or exacerbation of existing tics, transient depressed moods, cerebral arteritis and/or occlusion, Tourette's syndrome, toxic psychosis (sometimes with visual and tactile hallucinations).

Very rare reports of poorly documented neuroleptic malignant syndrome (NMS) have been received. In most of these reports patients were also receiving other medications. It is uncertain what role methylphenidate hydrochloride played in these cases.

### Gastrointestinal System

Common: nausea, vomiting and abdominal pain may occur at the start of treatment and may be alleviated if taken with food. Dry mouth.

Very rare: abnormal liver function, ranging from transaminase elevation to hepatic coma.

### Cardiovascular System

Common: palpitations, changes in blood pressure and heart rate (usually an increase), tachycardia, cardiac arrhythmias.

Rare: Angina pectoris.

### Skin And/Or Hypersensitivity Reactions

Common: rash, pruritus, urticaria, fever, arthralgia, scalp hair loss.

Very rare: exfoliative dermatitis, erythema multiforme, thrombocytopenic purpura.

### Hematologic System

Very rare: leukopenia, thrombocytopenia, anemia.

### Miscellaneous

Rare: moderately reduced weight gain and slight growth retardation during prolonged use in children.

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

### **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system 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.

Management consists in providing supportive measures. The patient must be protected against self-injury and against external stimuli that would exacerbate overstimulation already present. If signs and symptoms are not too severe and the patient is conscious, gastric contents may be evacuated by induction of emesis or gastric lavage. In the presence of severe intoxication, use a carefully titrated dosage of short-acting barbiturate before performing gastric lavage.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required to reduce hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for methylphenidate hydrochloride overdosage has not been established.

## **DOSAGE AND ADMINISTRATION**

Dosage of APO-METHYLPHENIDATE (methylphenidate hydrochloride) should be individualized according to the needs and responses of the patient.

### **Children (6 Years And Over)**

**APO-METHYLPHENIDATE Tablets:** APO-METHYLPHENIDATE should be initiated in small doses, (e.g. 5-10 mg TID) with weekly increments of 5 to 10 mg in the daily dosage. Dosage should be individualized on the basis of factors such as age, body weight and individual response. Timing of drug administration should be aimed to coincide with periods of greatest academic, behavioural and social stress.

Daily dosage above 60 mg is not recommended.

If symptoms do not improve after dose titration over a one month period, the drug should be discontinued.

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

**APO-METHYLPHENIDATE SR (extended-release) Tablets:** APO-METHYLPHENIDATE SR tablets have a duration of action of approximately 8 hours. Therefore, APO-METHYLPHENIDATE SR tablets may be used in place of APO-METHYLPHENIDATE tablets when the 8-hour dosage of APO-METHYLPHENIDATE SR corresponds to the titrated 8-hour dosage of APO-METHYLPHENIDATE. APO-METHYLPHENIDATE SR tablets must be swallowed whole and never be crushed or chewed.

If paradoxical aggravation of symptoms or other adverse events occur, reduce dosage or if necessary, discontinue drug.

APO-METHYLPHENIDATE should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

### Adults

APO-METHYLPHENIDATE Tablets: Administer in divided doses 2 or 3 times daily. Average daily dosage is 20 to 30 mg. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day, should take the last dose before 6 p.m.

APO-METHYLPHENIDATE SR (extended-release) Tablets: APO-METHYLPHENIDATE SR tablets have a duration of action of approximately 8 hours. Therefore, APO-METHYLPHENIDATE SR tablets may be used in place of APO-METHYLPHENIDATE tablets when the 8-hour dosage of APO-METHYLPHENIDATE SR corresponds to the titrated 8-hour dosage of APO-METHYLPHENIDATE. APO-METHYLPHENIDATE SR tablets must be swallowed whole and never be crushed or chewed.

## **PHARMACEUTICAL INFORMATION**

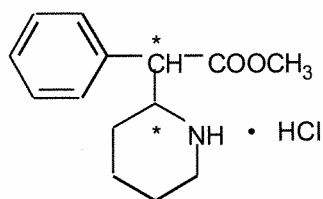
### Drug Substance

Proper Name: methylphenidate hydrochloride



- Chemical names:
- 1) 2-Piperidineacetic acid,  $\alpha$ -phenyl-, methyl ester, hydrochloride, (R\*,R\*)-( $\pm$ )-
  - 2) Methyl  $\alpha$ -phenyl-2-piperidineacetate hydrochloride

Structural Formula:



Molecular formula:  $C_{14}H_{19}NO_2HCl$

Molecular weight: 269.8

Description: White, odorless, fine crystalline powder, solutions which are acid to litmus

Solubility: Freely soluble in water

### Composition

APO-METHYLPHENIDATE (methylphenidate hydrochloride) 10 mg Tablets: In addition to 10 mg of methylphenidate hydrochloride, each tablet contains the non-medicinal ingredients anhydrous lactose, magnesium stearate, D&C yellow #10 and FD&C blue #1.

APO-METHYLPHENIDATE (methylphenidate hydrochloride) 20 mg Tablets: In addition to 20 mg of methylphenidate hydrochloride, each tablet contains the non-medicinal ingredients anhydrous lactose, magnesium stearate and D&C yellow #10.

APO-METHYLPHENIDATE SR (methylphenidate hydrochloride) 20 mg Tablets: In addition to 20 mg of methylphenidate hydrochloride, each tablet contains the non-medicinal ingredients hydroxypropyl methylcellulose, magnesium stearate and colloidal silicon dioxide.

#### Stability And Storage Recommendations

Protect from heat (store between 15 and 30°C) and humidity.

Keep out of reach of children.

#### **AVAILABILITY OF DOSAGE FORMS**

APO-METHYLPHENIDATE tablets 10 mg: each pale blue, round, flat-faced, bevelled-edge tablet, scored and engraved “MET” over “10” on one side and “APO” on the other contains 10 mg methylphenidate hydrochloride. Available in bottles of 100 and 500.

APO-METHYLPHENIDATE tablets 20 mg: each pale yellow, round, flat-faced, bevelled-edge tablet, scored and engraved “MET” over “20” on one side and “APO” on the other contains 20 mg methylphenidate hydrochloride. Available in bottles of 100 and 500.

APO-METHYLPHENIDATE SR tablets 20 mg: each white to off-white, biconvex tablet, engraved “APO” on one side, “M” over “20” on the other contains 20 mg methylphenidate hydrochloride. Available in bottles of 100.

APO-METHYLPHENIDATE is a controlled drug.

## **INFORMATION FOR THE PATIENT**

### Introduction

APO-METHYLPHENIDATE is used in two different medical conditions: 1) Attention-Deficit Hyperactivity Disorder (ADHD) and 2) Narcolepsy. Information on the use of APO-METHYLPHENIDATE in each of these conditions is given in separate sections of this leaflet. Please refer to **either** APO-METHYLPHENIDATE In Attention-Deficit Hyperactivity Disorder - Information For The Parents or APO-METHYLPHENIDATE In Narcolepsy - Information For The Patient for information suited to your needs.

### APO-METHYLPHENIDATE In Attention-Deficit Hyperactivity Disorder

#### Information For The Parents

The doctor has prescribed APO-METHYLPHENIDATE for your child's behavioural condition known as Attention-Deficit Hyperactivity Disorder (ADHD). The following information will tell you about ADHD and the use of APO-METHYLPHENIDATE in this condition. If you want to know more or have any questions, please ask the doctor or pharmacist.

#### About Attention-Deficit Hyperactivity Disorder (ADHD)

ADHD is a behavioural disorder in children and adolescents. It has been called by many other names including: Attention Deficit Disorder, Hyperkinetic Disorder, Minimal Brain Dysfunction, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction and Psycho-organic Syndrome of Children.

Children who suffer from ADHD show behavioural problems such as difficulty concentrating, impulsiveness and restlessness. They may fail at school although they may have adequate intelligence. Such children may be unpopular among children of the same age because of their clumsiness, intrusive behaviour and failure to follow the rules of games. Many prefer to be friends with younger children. Parents often feel that these children need more coaching and supervising than their brothers and sisters in most daily activities. Discipline usually cannot change such children's behaviour. Teachers complain about their disruptiveness and constant need for attention. Most children with ADHD do not complain of any problems; therefore, these children may not receive medical help unless the teacher(s) or parent(s) are aware of the nature of the problem. Medical exams, psychological and educational tests are all necessary in diagnosing ADHD.

#### About The Use Of APO-METHYLPHENIDATE In Attention-Deficit Hyperactivity Disorder (ADHD)

APO-METHYLPHENIDATE belongs to a group of medicines called central nervous system stimulants. When used in ADHD, APO-METHYLPHENIDATE improves behaviour by reducing restlessness and increasing attention. APO-METHYLPHENIDATE, however, will not cure ADHD. Treatment with APO-METHYLPHENIDATE or other stimulants should always be combined with other treatment measures, such as psychological counselling and educational tutoring by skilled and experienced therapists.

There is no evidence that children with ADHD become addicted to APO-METHYLPHENIDATE, or that they tend to abuse drugs later in life. Central nervous stimulants, including APO-METHYLPHENIDATE should only be given under close medical supervision to patients whose condition has been properly diagnosed.

### How APO-METHYLPHENIDATE Should Be Taken

APO-METHYLPHENIDATE comes in tablets to be taken by mouth. The doctor determines how much and how often your child should take APO-METHYLPHENIDATE according to their individual needs. In order for your child to receive the most benefits from APO-METHYLPHENIDATE, it is important that APO-METHYLPHENIDATE be taken only as directed by the doctor. Take only the amount of medication at the time intervals and for the time period that the doctor has prescribed. Your child should not take more than 60 mg of APO-METHYLPHENIDATE per day. If APO-METHYLPHENIDATE SR (extended-release) tablets have been prescribed for your child, these tablets must be swallowed whole and never be crushed or chewed.

### What You Should Be Aware Of

Use of APO-METHYLPHENIDATE may be unsuitable or require special attention under certain medical conditions. You should let the doctor know if your child has conditions such as a previous allergy to APO-METHYLPHENIDATE or any of its components, high blood pressure, heart disorders, thyroid disorders, glaucoma (increased eye pressure), epilepsy, agitation, tension, motor tics or family history or diagnosis of Tourette's syndrome, depression, or a history of severe depression, psychosis, anxiety, drug or alcohol abuse, or other medical problems. Alcohol should be avoided. APO-METHYLPHENIDATE may increase seizures in some patients with a history of seizures.

**APO-METHYLPHENIDATE should not be used in children under 6 years of age.**

It is important to tell the doctor and pharmacist if your child takes other medications besides APO-METHYLPHENIDATE since combining drugs can sometimes result in changing the expected drug effects or cause harmful effects.

Get medical help immediately in cases of overdose.

### Possible Unwanted Effects

**Contact the doctor if your child experiences any of the following unwanted effects:** sudden high fever, fast heartbeat, breathing difficulties, chest pain, sweating, vomiting, bruising, muscle twitching or tics, sore throat and fever, confusion, hallucination and convulsions. Other side effects not listed above may occur in some patients. If you notice any other effects, tell your doctor immediately.

Your child may experience stomach discomfort, nausea and/or loss of appetite with APO-METHYLPHENIDATE. These problems may go away with time.

Taking APO-METHYLPHENIDATE with food may reduce stomach discomfort.

APO-METHYLPHENIDATE may reduce weight gain or growth in children. To help restrict this problem to a minimum, the doctor may want to withhold APO-METHYLPHENIDATE over weekends and during vacations.

APO-METHYLPHENIDATE may cause sleeplessness if taken too close to bedtime.

### How APO-METHYLPHENIDATE Should Be Stored

Protect APO-METHYLPHENIDATE from moisture and heat. Store between 15 and 30°C.

Keep out of reach of children.

### Further Information

Remember to take back unused medicine to your pharmacist.

### Other Important Information

Use this medicine only as directed by your doctor. Do not take more of it, do not take it more often, and do not take it for a longer time than your doctor ordered.

APO-METHYLPHENIDATE SR tablets must be swallowed whole and never broken before taking them.

### APO-METHYLPHENIDATE In Narcolepsy

#### Information For The Patient

The doctor has prescribed APO-METHYLPHENIDATE for your medical condition known as narcolepsy. The following information will tell you about narcolepsy and the use of APO-METHYLPHENIDATE in this condition. If you want to know more or have any questions, please ask the doctor or pharmacist.

### About Narcolepsy

Persons who suffer from narcolepsy experience attacks of sleepiness during the day although they may have enough sleep at night. These attacks usually occur in unusual situations such as standing, eating or the middle of a conversation. Some people find their head falling forward, jaw dropping, knees buckling or even falling to the ground while they are conscious. These attacks may be brought on by emotional situations such as hearty laughter, excitement, sadness or anger.

### About The Use Of APO-METHYLPHENIDATE In Narcolepsy

APO-METHYLPHENIDATE belongs to a group of medicines called central nervous system stimulants. When used in narcolepsy, APO-METHYLPHENIDATE may relieve the inappropriate daytime sleepiness; however, many people suffering from narcolepsy need additional treatment aimed at other aspects of this condition.

### How APO-METHYLPHENIDATE Should Be Taken

APO-METHYLPHENIDATE comes in tablets to be taken by mouth. Your doctor determines how much and how often you should take APO-METHYLPHENIDATE according to your individual needs. In order for you to receive the most benefits from APO-METHYLPHENIDATE, it is important that APO-METHYLPHENIDATE be taken only as directed by your doctor. Take only the amount of medication at the time intervals, and for the time period that your doctor has prescribed. If APO-METHYLPHENIDATE SR (extended release) tablets have been prescribed for you, these tablets should never be crushed or chewed.



### What You Should Be Aware Of

APO-METHYLPHENIDATE should not be used to relieve normal tiredness.

Use of APO-METHYLPHENIDATE may be unsuitable or require special attention under certain medical conditions. You should let the doctor know if you have conditions such as a previous allergy to APO-METHYLPHENIDATE or any of its components, high blood pressure, heart disorders, thyroid disorders, glaucoma (increased eye pressure), epilepsy, agitation, tension, motor tics or family history or diagnosis of Tourette's syndrome, depression, or a history of severe depression, psychosis, anxiety, drug or alcohol abuse, or other medical problems. Alcohol should be avoided. APO-METHYLPHENIDATE may increase seizures in some patients with a history of seizures.

### Tell your Doctor if you are pregnant or breast-feeding.

APO-METHYLPHENIDATE SHOULD NOT BE USED DURING PREGNANCY. MOTHERS TAKING APO-METHYLPHENIDATE SHOULD NOT BREAST-FEED THEIR BABIES.

It is important to tell your doctor and pharmacist if you take other medications besides APO-METHYLPHENIDATE since combining drugs can sometimes result in changing the expected drug effects or cause harmful effects. Alcohol should be avoided.

APO-METHYLPHENIDATE may affect your ability to drive or operate machinery.

Get medical help immediately in cases of overdose.

### Possible Unwanted Effects

You may experience stomach discomfort, nausea and/or loss of appetite with APO-METHYLPHENIDATE. These problems may go away with time. Taking APO-METHYLPHENIDATE with food may reduce stomach discomfort.

Weight loss may occur when APO-METHYLPHENIDATE is taken over a long period of time.

APO-METHYLPHENIDATE may cause sleeplessness if taken too close to bedtime.

Contact your doctor immediately if you experience any of the following unwanted effects: sudden high fever, fast heartbeat, breathing difficulties, chest pain, sweating, vomiting, bruising, muscle twitching or tics, sore throat and fever, confusion, hallucination and convulsions. Other side effects not listed above may occur in some patients. If you notice any other effects, tell your doctor immediately.

### How APO-METHYLPHENIDATE Should Be Stored

Protect APO-METHYLPHENIDATE from moisture and heat. Store between 15 and 30°C.

**Keep out of reach of children.**

### Further Information

Remember to take back unused medicine to your pharmacist.

### Other Important Information

Use this medicine only as directed by your doctor. Do not take more of it, do not take it more often, and do not take it for a longer time than your doctor ordered.

APO-METHYLPHENIDATE SR tablets must be swallowed whole and never broken before taking them.

## **TOXICOLOGY**

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/day. This dose is approximately 30 times and 2.5 times the maximum recommended human dose on a mg/kg and mg/m<sup>2</sup> basis, respectively.

Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 4 times the maximum recommended human dose on a mg/kg and mg/m<sup>2</sup> basis, respectively.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response in an *in vitro* assay in Chinese Hamster Ovary (CHO) cells. The genotoxic potential of methylphenidate hydrochloride has not been evaluated in an *in vitro* assay.

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