PRODUCT MONOGRAPH

NTP-METHYLPHENIDATE ER-C

(Methylphenidate Hydrochloride)

Extended-release Tablets 18 mg, 27 mg, 36 mg, and 54 mg

NT Pharma Standard

CNS Stimulant

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Extended release tablet / 18mg, 27mg, 36mg and 54 mg	Lactose Monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section*

INDICATIONS AND CLINICAL USE

NTP-METHYLPHENIDATE ER-C (methylphenidate hydrochloride extended-release) is indicated for treatment of Attention Deficit Hyperactivity Disorder (ADHD) in:

- Children (6 – 12 years of age)
- Adolescents (13 – 18 years of age)
- Adults (> 18 years of age)

Paediatrics (< 6 years of age):
NTP-METHYLPHENIDATE ER-C should not be used in children under six years, since safety and efficacy in this age group have not been established.

Geriatrics (> 65 years of age):
No data available.

A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and that 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 must be present in 2 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 6 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 6 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

The specific etiology of ADHD 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

NTP-METHYLPHENIDATE ER-C 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 drug treatment medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Long-Term Use

The effectiveness of methylphenidate hydrochloride extended release for long-term use, i.e. for more than 4 weeks in children and adolescents or 5 weeks in adults, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use NTP-METHYLPHENIDATE ER-C for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

- Anxiety, tension, agitation, thyrotoxicosis, advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension or glaucoma.

- Patients who are hypersensitive to methylphenidate or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

- Patients with motor tics or with a family history or diagnosis of Tourette's syndrome (verbal tics) (see **ADVERSE REACTIONS**).

- 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) (see **DRUG INTERACTIONS; Drug-Drug Interactions**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
• **Drug Dependence** (see **Dependence/Tolerance** section below)

General

NTP-METHYLPHENIDATE ER-C is intended for oral use only. In dogs, the intravenous injection of the pulverized methylphenidate hydrochloride extended-release tablets resulted in death (see ***Product Monograph Part II*: TOXICOLOGY, Acute Toxicity**).

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with stimulant drugs used for ADHD treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious cardiac problems. Although some serious heart problems alone carry an increased risk of sudden death, NTP-METHYLPHENIDATE ER-C generally should not be used in children, adolescents, or adults with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults

Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs (see **CONTRAINDICATIONS**).

General

Children: 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

sudden/cardiac death 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 other sympathomimetic ADHD drugs or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment with sympathomimetic medications, a personal and family history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during ADHD treatment should undergo a prompt cardiac evaluation.

Fatigue
NTP-METHYLPHENIDATE ER-C should not be used for the prevention or treatment of normal fatigue states.

Information for Patients
Patients should be informed that NTP-METHYLPHENIDATE ER-C should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. Patient information is provided in ***Product Monograph Part III*: CONSUMER INFORMATION**. To assure safe and effective use of NTP-METHYLPHENIDATE ER-C, the information and instructions provided in ***Product Monograph Part III*: CONSUMER INFORMATION** should be discussed with patients.

Carcinogenesis and Mutagenesis
See ***Product Monograph Part II*: TOXICOLOGY; Carcinogenicity and Mutagenicity** and **Reproductive and Developmental Toxicity** for discussion on animal data.

Cardiovascular
Pre-existing Cardiovascular and Cerebral Vascular Conditions CNS stimulants should be used with caution in patients with a pre-existing cardiovascular or cerebrovascular condition, taking into account risk predictors for these conditions. Patients should be screened for pre-existing or underlying cardiovascular or cerebrovascular conditions before initiation of treatment with NTP-METHYLPHENIDATE ER-C and monitored for new conditions of the heart or brain during the course of treatment.

Hypertension and Other Cardiovascular Conditions
NTP-METHYLPHENIDATE ER-C should be used cautiously in patients with mild hypertension and other cardiovascular conditions. Blood pressure should be monitored at appropriate intervals in patients receiving NTP-METHYLPHENIDATE ER-C, especially in patients with hypertension. In the laboratory classroom clinical trials in children (Studies 1 and 2), both methylphenidate hydrochloride extended release and methylphenidate t.i.d. increased resting pulse by an average of 2-6 beats per minute (bpm) and produced average increases of systolic blood pressure (sbp) and diastolic blood pressure (dbp) of approximately 1-4 mm Hg during the

day, relative to placebo. In the double-blind, placebo-controlled study in adults (Study 5), changes in mean DBP and SBP were observed with methylphenidate hydrochloride extended-release doses up to 72 mg. A statistically significant ($p<0.05$) mean increase in standing DBP and SBP versus baseline was reached at Week 1 in the 72 mg methylphenidate hydrochloride extended-release dose group (mean increase of 2.0 mm Hg for standing DBP and 4.0 mm Hg for standing and supine SBP) but not at later time points. A statistically significant increase in pulse was observed for all methylphenidate hydrochloride extended-release dose groups (18 mg, 36 mg and 72 mg) versus baseline (range of mean increase of 2.0-10.6 bpm). Therefore, caution is advised 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 or recent myocardial infarction.

Dependence/Tolerance

Drug Dependence

NTP-METHYLPHENIDATE ER-C 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 behaviour. Frank psychotic episodes can occur, especially with parenteral abuse (See **DOSAGE AND ADMINISTRATION, Administration**). Careful supervision is required during withdrawal from abuse since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of an underlying disorder that may require follow-up.

Endocrine and Metabolism

Long-Term Suppression of Growth

Sufficient data on the safety of long-term use of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (i.e. weight gain and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted.

Gastrointestinal

Potential for Gastrointestinal Obstruction

Because the NTP-METHYLPHENIDATE ER-C tablet does not appreciably change in shape in the gastrointestinal tract, NTP-METHYLPHENIDATE ER-C should not be administered to patients with pre-existing gastrointestinal narrowing (pathologic or iatrogenic, such as small bowel inflammatory disease, “short gut” syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudo-obstruction, or Meckel’s diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations. There have been very rare reports of obstructive symptoms associated with the use of methylphenidate hydrochloride extended release in patients without known gastrointestinal stricture. Due to the controlled-release design, NTP-METHYLPHENIDATE ER-C tablets should only be used in patients who are able to swallow the tablets whole (see **DOSAGE AND ADMINISTRATION; Administration**).

Neurologic

Seizures

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with a prior history of seizures, in patients with prior EEG abnormalities in the absence of seizures, and, very rarely, in the absence of history of seizures and no prior EEG evidence of seizures. In the presence of seizures or suspected seizures, the drug should be discontinued.

Effects on Ability to Drive and Use Machines

Stimulants may impair the ability of the patient to operate potentially hazardous machinery or vehicles. Patients should be cautioned accordingly until they are reasonably certain that NTP-METHYLPHENIDATE-ER-C does not adversely affect their ability to engage in such activities.

Ophthalmologic

Visual Disturbance

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

Psychiatric

Pre-Existing Psychosis

Administration of stimulants may exacerbate symptoms of behaviour disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression

Aggressive behaviour or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants

cause aggressive behaviour or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behaviour or hostility.

Special Populations

Pregnant Women: Methylphenidate hydrochloride has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of methylphenidate hydrochloride extended release on a mg/kg and mg/m^2 basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite alpha-phenyl-2-piperidine acetic acid (PPAA) in pregnant rats was 2 times that seen in trials in volunteers and patients with the maximum recommended dose of methylphenidate hydrochloride extended release based on the AUC.

There are no adequate and well-controlled studies in pregnant women. NTP-METHYLPHENIDATE ER-C should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: A study conducted in rats indicated that the distribution profiles of methylphenidate in milk and plasma are similar. It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, NTP-METHYLPHENIDATE ER-C should not be administered to a nursing woman unless the anticipated benefits to the mother outweigh the potential hazards to the infant.

Pediatrics (< 6 years of age):

NTP-METHYLPHENIDATE ER-C should not be used in children under six years, since safety and efficacy in this age group have not been established. Long-term effects of methylphenidate in children have not been well established (see **WARNINGS AND PRECAUTIONS**; **Endocrine and Metabolism**).

Monitoring and Laboratory Tests

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

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The development program for methylphenidate hydrochloride extended release included exposures in a total of 2227 participants in clinical trials. The patients in these studies received methylphenidate hydrochloride extended release 18, 36, 54 or 72 mg/day. Children, adolescents and adults with ADHD were evaluated in five placebo-controlled clinical studies (Studies 1, 2 and 3 in children; Study 4 in adolescents; Study 5 in adults), three open-label clinical trials and two open-label extensions. A limited number of adolescents and adults received methylphenidate hydrochloride extended release 72 mg/day or 90 mg/day, respectively. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events, except for Study 5 in adults, where MedDRA terminology was used.

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 Events Leading to Discontinuation of Treatment

In a 4-week placebo-controlled, parallel-group trial (Study 3), one patient treated with methylphenidate hydrochloride extended release (0.9%; 1/106), one methylphenidate t.i.d.-treated patient (0.9%; 1/107), and one placebo-treated patient (1.0%; 1/99) discontinued due to an adverse event (sadness, emotional lability, and increase in tics, respectively).

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

In the 5-week placebo-controlled phase of a trial in adults (Study 5), 0% (0/96) of the patients in the placebo group, 1.0% (1/101) of the patients in the methylphenidate hydrochloride extended release 18 mg dose group, 2.9% (3/102) of the patients in the methylphenidate hydrochloride extended release 36 mg dose group and 7.8% (8/102) of the patients in the methylphenidate hydrochloride extended release 72 mg dose group discontinued due to an adverse event.

In two open-label, long-term safety trials (Studies 6 and 7), one study up to 27 months in children aged 6 to 13 and one study up to 9 months in child, adolescent and adult patients treated with methylphenidate hydrochloride extended release, 6.7% (101/1514) of patients discontinued due to adverse events. Those events leading to discontinuation of methylphenidate hydrochloride extended release, with an incidence of >0.5%, included: insomnia (1.5%),

twitching (tics, 1.0%), nervousness (0.7%), emotional lability (0.7%), abdominal pain (0.7%), and anorexia (0.7%).

Adverse Events Occurring in Patients Treated with Methylphenidate Hydrochloride Extended Release

Table 1.1 enumerates, for the 4-week placebo-controlled, parallel-group trial in children with ADHD at methylphenidate hydrochloride extended release doses of 18, 36, or 54 mg q.d., the incidence of treatment-emergent adverse events. The table includes only those events that occurred in 1% or more of patients treated with methylphenidate hydrochloride extended release, methylphenidate hydrochloride and placebo-treated patients.

Table 1.1: Incidence (%) of Treatment-Emergent Events[1] in a 4-Week Placebo-Controlled Clinical Trial of Methylphenidate Hydrochloride Extended Release in Children

Body Systems	**Preferred Term[2]**	**Methylphenidate Hydrochloride Extended Release, q.d.** (n = 106)	**Methylphenidate hydrochloride t.i.d.** (n = 107)	**Placebo** (n = 99)
General	Headache	14	6	10
	Abdominal pain	7	6	1
	Aggravation reaction	2	2	2
Digestive	Vomiting	4	2	3
	Anorexia	4	0	0
Nervous	Insomnia	4	1	1
	Dizziness	2	0	0
Respiratory	Upper respiratory tract infection	8	7	5
	Cough increased	4	8	2
	Pharyngitis	4	4	3
	Sinusitis	3	1	0

[1]Events, regardless of causality, for which the incidence for patients treated with methylphenidate hydrochloride extended release was at least 1%. Incidence greater than 1% has been rounded to the nearest whole number.
[2] COSTART terms

Table 1.2 lists the incidence of treatment-emergent adverse events for a 2-week placebo-controlled trial (Study 4) in adolescents with ADHD at methylphenidate hydrochloride extended release doses of 18, 36, 54 or 72 mg/day.

Table 1.2: Incidence (%) of Treatment-Emergent Events[1] in a 2-Week Placebo-Controlled Clinical Trial of Methylphenidate Hydrochloride Extended Release in Adolescents

Body Systems	Preferred Term[2]	methylphenidate hydrochloride extended release, q.d. (n=87)	Placebo (n=90)
General	Abdominal Pain	2	2
	Accidental Injury	6	3
	Allergic Reaction	1	0
	Asthenia	2	2
	Chest Pain	1	0
	Fever	3	0
	Flu Syndrome	1	0
	Headache	9	8
	Infection	1	6
	Pain	1	1
Digestive	Anorexia	2	0
	Diarrhoea	2	0
	Dyspepsia	1	0
	Gastrointestinal Disorder	1	0
	Increased Appetite	1	0
	Nausea	1	2
	Tooth Caries	1	0
	Vomiting	3	0
Musculoskeletal	Myalgia	1	0
Nervous	Agitation	1	0
	Anxiety	1	0
	Dizziness	1	0
	Insomnia	4	0
	Neurosis	1	1
	Tremor	1	0
Respiratory	Pharyngitis	2	1
	Rhinitis	3	2
Urogenital	Dysmenorrhoea	2	0

[1] Events, regardless of causality, for which the incidence for patients treated with methylphenidate hydrochloride extended release was at least 1%. Incidence has been rounded to the nearest whole number.
[2] COSTART terms

Table 1.3 lists the incidence of treatment-emergent adverse events for a 5-week placebo-controlled trial (Study 5) in adults with ADHD at methylphenidate hydrochloride extended release doses of 18, 36, or 72 mg/day.

Table 1.3: Incidence (%) of Treatment-Emergent Events1 in a 5-Week Placebo-Controlled Clinical Trial of Methylphenidate Hydrochloride Extended Release in Adults

Body Systems	Preferred Term[2]	methylphenidate hydrochloride extended release			Placebo
		18 mg q.d. (n=101)	36 mg q.d. (n=102)	72 mg q.d. (n=102)	q.d. (n=96)
Cardiac Disorders	Palpitations	2	5	5	0
	Tachycardia	4	5	8	0
Ear and Labyrinth Disorders	Vertigo	2	3	2	0
Gastrointestinal Disorders	Abdominal Pain Upper	4	2	2	5
	Diarrhea	3	1	4	5
	Dry Mouth	8	7	21	2
	Hemorrhoids	0	0	4	0
	Nausea	8	16	15	4
General Disorders and Administration Site Conditions	Fatigue	4	4	6	6
Infectious and Infestations	Influenza	4	2	2	3
	Nasopharyngitis	7	8	4	9
Investigations	Weight Decreased	3	8	11	5
Metabolism and Nutrition Disorders	Decreased Appetite	20	22	34	7
Nervous System Disorders	Confusional State	0	3	1	0
	Dizziness	6	10	9	7
	Headache	26	21	17	18
	Initial Insomnia	3	2	5	2
	Insomnia	12	12	17	7
	Migraine	0	1	3	3
	Paresthesia	3	1	1	0
	Tremor	1	1	7	1
Psychiatric Disorders	Aggression	2	3	2	1
	Agitation	0	1	3	1
	Anxiety	3	5	8	1
	Attention Deficit/ Hyperactivity Disorder	0	0	4	0
	Depressed Mood	6	3	5	1
	Depression	0	3	4	1
	Irritability	4	4	9	1
	Nervousness	0	3	8	1
	Restlessness	0	2	6	0
	Tension	0	3	0	0
Respiratory, Thoracic and Mediastinal Disorders	Pharyngolaryngeal Pain	2	0	4	1
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	5	3	8	1
Vascular Disorders	Hypertension	0	1	4	4

[1] Events, regardless of causality, for which the incidence in any methylphenidate hydrochloride extended release dosage group was at least 2%. Incidence has been rounded to the nearest whole number.
[2] MedDRA Terms

Adverse Events Occurring in Long-Term Safety Trials

Methylphenidate hydrochloride extended release was evaluated in two long-term open-label studies (n = 1514) up to 27 months. The adverse event profile seen is similar to that observed in shorter term trials. COSTART terminology is used to classify reported adverse experiences. The experiences are classified within body system categories and grouped by frequency.

Table 1.4: Adverse Events Occurring in Long-Term Safety Trials

Frequency	Very Frequent	Frequent		Less Frequent
Body System	**>10% - <50%**	**5-10%**	**<5% and ≥1%**	**<1%**
Body as a Whole	headache	accidental injury, abdominal pain, fever	flu syndrome, allergic reaction, infection, aggravation reaction, pain, extremity pain, back pain	surgery procedure, accidental overdose, chest pain, cyst, infection fungal, photosensitivity reaction, malaise, asthenia, neck pain
Cardiovascular System			hypertension	cardiovascular disorder, tachycardia, migraine
Digestive System		anorexia, vomiting	gastroenteritis, diarrhea, nausea, dyspepsia	rectal disorder, gastritis, increased appetite, nausea and vomiting, periodontal abscess, tongue disorder, tooth disorder, constipation
Endocrine System				diabetes mellitus
Hemic and Lymphatic System				ecchymosis, petechia, lymphadenopathy
Metabolic and Nutritional System			weight loss	dehydration
Musculoskeletal System			myalgia	arthralgia, leg cramps
Nervous System	insomnia		twitching, nervousness, emotional lability, anxiety, depression, somnolence, hostility, dizziness	apathy, neurosis, hallucinations, speech disorder, sleep disorder, tremor, thinking abnormal, abnormal dreams
Respiratory System	upper respiratory tract infection	pharyngitis, cough increased, rhinitis	sinusitis, respiratory disorder, asthma bronchitis, epistaxis	dyspnea, pneumonia, voice alterations, laryngitis
Skin System			rash, contact dermatitis	pustular rash, urticaria, eczema, pruritus, skin benign neoplasm, acne, alopecia, nail disorder, psoriasis, herpes simplex
Special Senses		otitis media	conjunctivitis	ear disorder, diplopia, ear pain
Urogenital System				albuminuria, urinary frequency, urinary tract infection, urinary urgency

Tics

During two long-term, open-label studies, the overall incidence of tics (twitching) in children was 4.3% (48/1109 subjects). In one study, the incidence of tics rose from 3% at baseline to 5% after one month. The incidence remained the same during the rest of the study. Treatment period was up to 27 months with mean treatment duration of 10.3 months.

In a long-term study, of up to 9 months of treatment, the incidence of tics was 0.4% (1/269) in adolescents was 0.7% (1/136) in adults.

Post-Market Adverse Drug Reactions

Adverse events reported since market introduction in patients taking methylphenidate hydrochloride extended release include palpitations, cardiac arrhythmia, sudden cardiac death, suicide, suicide ideation, suicide attempt, exfoliative dermatitis, Stevens-Johnson Syndrome, emerging psychosis, seizure, dyskinesia, pancreatitis, aplastic anaemia, serum sickness, hypoglycaemia, abnormal liver function tests (e.g., transaminase elevation), leukopenia, thrombocytopenia, transient pancytopenia, difficulties in visual accommodation, blurred vision. The causal relationship between methylphenidate hydrochloride extended release and the emergence of these events has not been established.

Adverse Events with Other Methylphenidate Hydrochloride Products

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, e.g., hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anaemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

DRUG INTERACTIONS

Overview

Alcohol may exacerbate the CNS adverse effect of psychoactive drugs. Therefore, patients undergoing NTP-METHYLPHENIDATE ER-C therapy should be advised to avoid alcohol during treatment.

Because of possible increases in blood pressure and heart rate, NTP-METHYLPHENIDATE ER-C should be used cautiously with drugs with similar pharmacological actions.

Drug-Drug Interactions

Inhibition of Drug Metabolism by Methylphenidate Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants (e.g., warfarin), anticonvulsants (e.g., phenobarbital, phenytoin, primidone) and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times) when initiating or discontinuing concomitant methylphenidate.

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 precautions apply to NTP-METHYLPHENIDATE ER-C (see **CONTRAINDICATIONS**).

Clonidine
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.

Drug-Food Interactions
There are no known food interactions with methylphenidate hydrochloride extended release.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

NTP-METHYLPHENIDATE ER-C 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 methylphenidate hydrochloride extended release varies widely.

NTP-METHYLPHENIDATE ER-C 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 AND PRECAUTIONS**).

Children: 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 sudden/cardiac death 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 other sympathomimetic ADHD drugs or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment with sympathomimetic medications, a personal and family history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during ADHD treatment should undergo a prompt cardiac evaluation. Patients who are considered to need extended treatment with NTP-METHYLPHENIDATE ER-C should undergo periodic evaluation of their cardiovascular status (see **WARNINGS AND PRECAUTIONS**).

Recommended Dose and Dosage Adjustment

General

NTP-METHYLPHENIDATE ER-C should be administered orally once daily in the morning, with or without food. For patients new to methylphenidate, the starting dose for NTP-METHYLPHENIDATE ER-C should be 18 mg daily. For patients currently on a methylphenidate-based product, see the conversion table below.

Initial Dose Selection

Patients New to Methylphenidate

The recommended starting dose of NTP-METHYLPHENIDATE ER-C for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily.

Table 1.5: Recommended starting dose and maximum dosage of NTP-METHYLPHENIDATE ER-C for patients new to methylphenidate

Patient Age	Recommended Starting Dose	Maximum Dosage
Children (6-12 years of age)	18 mg/day	54 mg/day
Adolescents (13-18 years of age)	18 mg/day	54 mg/day
Adolescents (>18 years of age)	18 mg/day	72 mg/day

A limited number of adolescents have been treated with methylphenidate hydrochloride extended release 72 mg/day in the open-label extension of Study 4 (n = 62). A limited number of adults have been treated with doses up to 90 mg/day in the open-label extension of Study 5 (n = 41).

Patients Currently Using Methylphenidate Hydrochloride

The recommended conversion dose of NTP-METHYLPHENIDATE ER-C for patients who are currently taking methylphenidate hydrochloride b.i.d., t.i.d., or sustained-release (SR) at doses of 10 to 60 mg/day is provided in Table 1.6. Dosing recommendations are based on current dose regimen and clinical judgment.

Table 1.6: Recommended Dose Conversion from Methylphenidate Hydrochloride Regimens to NTP-METHYLPHENIDATE ER-C

Previous Methylphenidate Hydrochloride Daily Dose	**Recommended NTP-METHYLPHENIDATE ER-C Initial Dose**
5 mg methylphenidate hydrochloride b.i.d./t.i.d. or 20 mg methylphenidate hydrochloride SR	18 mg q. a.m.
10 mg methylphenidate hydrochloride b.i.d./t.i.d.or 40 mg methylphenidate hydrochloride SR	36 mg q. a.m.
15 mg methylphenidate hydrochloride b.i.d./t.i.d. or 60 mg methylphenidate hydrochloride SR	54 mg q. a.m.

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

Dose Titration
Dosage should be individualized according to the needs and responses of the patient. Based on an assessment of clinical benefit and tolerability, doses may be adjusted at weekly intervals for patients who have not achieved an optimal response.

Maintenance/Extended Treatment
There is no evidence available from controlled trials to indicate how long the patient with ADHD should be treated with methylphenidate hydrochloride extended release tablets. It is generally agreed that pharmacological treatment of ADHD may be needed for extended periods. The physician who elects to use NTP-METHYLPHENIDATE ER-C for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy.

Dose Reduction and Discontinuation
If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced or, if necessary, the drug should be discontinued.

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

Administration

NTP-METHYLPHENIDATE ER-C tablets must be swallowed whole with liquids, and must not be chewed, divided or crushed. In dogs, the intravenous injection of the pulverized methylphenidate hydrochloride extended release tablets resulted in death (see ***Product Monograph Part II*: TOXICOLOGY, Acute Toxicity**).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Signs and Symptoms

Signs and symptoms of methylphenidate hydrochloride overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, muscle twitching, convulsions, grand mal convulsions, confusional state, hallucinations (auditory and/or visual), hyperhidrosis, headache, pyrexia, tachycardia, palpitations, heart rate increased, sinus arrhythmia, hypertension, mydriasis and dry mouth.

Recommended Treatment

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate the 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 pyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for methylphenidate hydrochloride extended release overdosage has not been established. The prolonged release of methylphenidate from NTP-METHYLPHENIDATE ER-C tablets should be considered when treating patients with overdose. Alcohol may induce the production of ethylphenidate. The amount of ethylphenidate production is proportional to the blood alcohol concentration (see **DRUG INTERACTIONS**; Overview). As with the management of all overdosage, the possibility of multiple drug ingestion, including alcohol, should be considered.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Methylphenidate hydrochloride is a central nervous system (CNS) stimulant. The mechanism of action on the CNS is not completely understood, but methylphenidate is thought to block the reuptake of dopamine and norepinephrine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Pharmacodynamics

Methylphenidate is a racemic mixture comprised of the *d*- and *l*-isomers. The *d*-isomer is pharmacologically active; the *l*-isomer has little pharmacologic activity. Following administration of methylphenidate hydrochloride extended release, plasma concentrations of the *l*-isomer were approximately 1/40th the plasma concentrations of the *d*-isomer.

Pharmacokinetics

Absorption: Methylphenidate is readily absorbed. Following oral administration of methylphenidate hydrochloride extended release, plasma methylphenidate concentrations reach an initial maximum at about 1 hour followed by gradual ascending concentrations over the next 5 to 9 hours. Mean times to reach peak plasma concentrations across all doses of methylphenidate hydrochloride extended release occurred between 6 to 10 hours. Methylphenidate hydrochloride extended release once daily (q.d.) minimizes the fluctuations between peak and trough concentrations associated with multiple doses of immediate-release methylphenidate treatments (see Figure 1.1). The relative bioavailability of methylphenidate hydrochloride extended release q.d. and methylphenidate three times a day (t.i.d.) in adults is comparable.

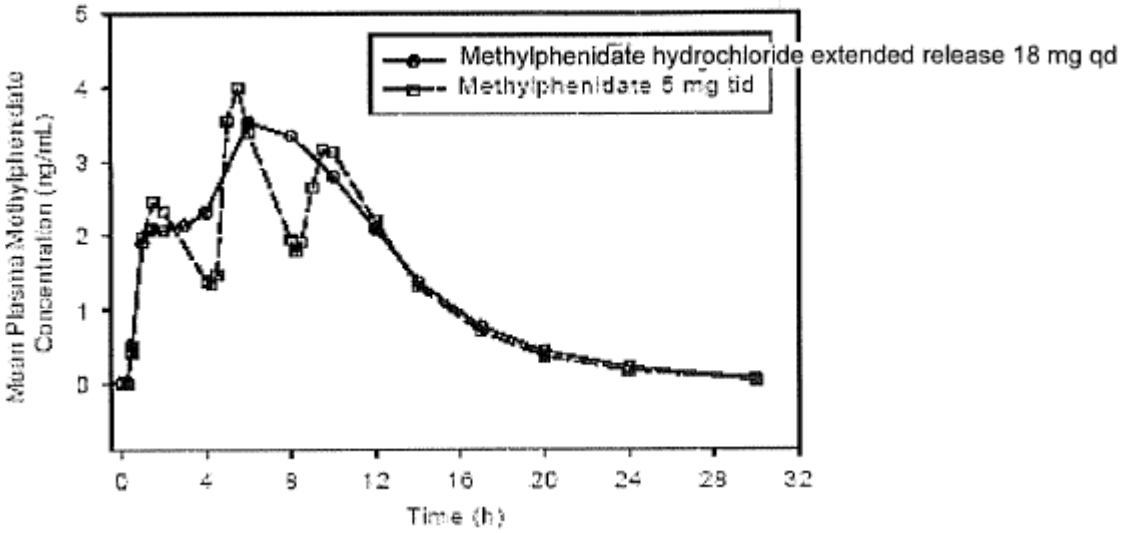


Figure 1.1: **Mean methylphenidate plasma concentrations in 36 fasted adults, following a single dose of methylphenidate hydrochloride extended release 18 mg q.d. and immediate-release methylphenidate hydrochloride 5 mg t.i.d. administered every 4 hours.**

Children (single dose)

The mean pharmacokinetic parameters in 13 children 7-12 years of age following administration of methylphenidate hydrochloride extended release 18, 36 or 54 mg are summarized in Table 1.7.

Table 1.7: Pharmacokinetic Parameters in Children after single dosing (Mean ± SD)

Parameters	Methylphenidate Hydrochloride Extended Release 18 mg (n = 3)	Methylphenidate Hydrochloride Extended Release 36 mg (n = 7)	Methylphenidate Hydrochloride Extended Release 54 mg (n = 3)
C_{max} (ng/mL)	6.0 ± 1.3	11.3 ± 2.6	15.0 ± 3.8
T_{max} (h)	9.4 ± 0.02	8.1 ± 1.1	9.1 ± 2.5
$AUC_{0\text{-}11.5}$ (ng·h/mL)#	50.4 ± 7.8	87.7 ± 18.2	121.5 ± 37.3

limited blood sampling

Adolescents (steady-state)

The pharmacokinetics of methylphenidate were evaluated in adolescents 13–16 years of age with ADHD following steady-state dosing with methylphenidate hydrochloride extended release 36 mg, 54 mg, or 72 mg. The mean pharmacokinetic parameters are summarized in Table 1.8.

Table 1.8: Pharmacokinetic Parameters in Adolescents at steady-state (Mean ± SD)

Parameters	Methylphenidate Hydrochloride Extended Release 36 mg (n = 10)	Methylphenidate Hydrochloride Extended Release 54 mg (n = 8)	Methylphenidate Hydrochloride Extended Release 72 mg* (n = 6)
Cmax (ng/mL)	9.9 ± 5.5	12.8 ± 3.4	17.8 ± 4.5
Tmax (h)	7.0 ± 2.1	6.8 ± 1.7	7.0 ± 1.8
AUCinf (ng·h/mL)	112 ± 55.9	141 ± 34.3	186 ± 33.9
t½ (h)	4.3 ± 2.0	3.6 ± 0.5	3.5 ± 0.5

* Not recommended. In the clinical study, only 62 adolescents received methylphenidate hydrochloride extended release at this dose level.

Adults

The mean single dose pharmacokinetic parameters in 36 healthy adults following the administration of methylphenidate hydrochloride extended release 18 mg q.d. and methylphenidate hydrochloride 5 mg t.i.d. are summarized in Table 1.9.

Table 1.9: Pharmacokinetic Parameters in Adult Subjects after Single Dosing (Mean ± SD)

Parameters	Methylphenidate Hydrochloride Extended Release (18 mg q.d.) (n = 36)	Methylphenidate Hydrochloride (5 mg t.i.d.) (n = 35)
C_{max} (ng/mL)	3.7 ± 1.0	4.2 ± 1.0
T_{max} (h)	6.8 ± 1.8	6.5 ± 1.8
AUC_{inf}(ng·h/mL)	41.8 ± 13.9	38.0 ± 11.0
$T_{½}$(h)	3.5 ± 0.4	3.0 ± 0.5

The mean single dose and steady-state pharmacokinetic parameters in 25 healthy adults following the administration of methylphenidate hydrochloride extended release 54 and 72 mg q.d. are summarized in Table 1.10.

Table 1.10: Pharmacokinetic Parameters in Adult Subjects Following Single Dose and at Steady-State (Mean ± SD)

Parameters	Methylphenidate Hydrochloride Extended Release	
	54 mg (n = 25)	72 mg (n = 25)
Single Dose		
C_{max}(ng/mL)	12.03 ± 3.54	17.12 ± 5.80
$T_{max\ a}$ (h)	6 (1-10)	6 (5-10)
AUC_{inf}(ng-h/mL)	130 ± 32.4	196 ± 65.7
$T_{½}$(h)	3.58 ± 0.629	3.57 ± 0.617
Steady State		
C_{max}(ng/mL)	12.45 ± 2.84	16.12 ± 4.60
T_{max} [a](h)	6 (1-10)	6 (5-8)
AUC_{tau}(ng-h/mL)	139 ± 33.6[b]	185 ± 49.0
$T_{½}$(h)	3.60 ± 0.844	3.63 ± 0.49

[a] median and range are listed
[b] N = 24

Distribution: Plasma methylphenidate concentrations in adults decline bi-exponentially following oral administration. The half-life of methylphenidate in adults following oral administration of methylphenidate hydrochloride extended release was approximately 3.5 h. In humans, 15 ± 5% of methylphenidate in the blood is bound to plasma proteins.

Metabolism and Excretion: In humans, methylphenidate is metabolized primarily by de-esterification to PPAA, which has little pharmacologic activity. In adults the metabolism of methylphenidate hydrochloride extended release q.d., as evaluated by metabolism to PPAA, is similar to that of methylphenidate t.i.d. The metabolism of single and repeated q.d. doses of methylphenidate hydrochloride extended release is similar. After oral dosing of radio-labelled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose (see **ACTION**

AND CLINICAL PHARMACOLOGY; Special Populations and Conditions, Renal Insufficiency).

Dose Proportionality
Following administration of methylphenidate hydrochloride extended release in single doses of 18, 36, and 54 mg/day to healthy adults, C_{max} and $AUC_{(0\text{-}inf)}$ of d-methylphenidate were proportional to dose, whereas l-methylphenidate C_{max} and $AUC_{(0\text{-}inf)}$ increased disproportionately with respect to dose. Following administration of methylphenidate hydrochloride extended release, plasma concentrations of the l-isomer were approximately 1/40th the plasma concentrations of the d-isomer.

In a multiple-dose study in adolescent ADHD patients aged 13 to 16 administered their prescribed dose (18 to 72 mg/day) of methylphenidate hydrochloride extended release, mean C_{max} and AUC_{tau} of d- and total methylphenidate increased proportionally with respect to dose.

Food Effects
In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of methylphenidate hydrochloride extended release when administered after a high fat breakfast. There is no evidence of dose dumping in the presence or absence of food.

Special Populations and Conditions
Gender: In healthy adults, the mean dose-adjusted $AUC_{(0\text{-}inf)}$ values for methylphenidate hydrochloride extended release were 36.7 ng•h/mL in men and 37.1 ng•h /mL in women, with no differences noted between the two groups.

Race: In adults receiving methylphenidate hydrochloride extended release tablets, dose-adjusted $AUC_{(0\text{-}inf)}$ was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age: The pharmacokinetics of methylphenidate hydrochloride extended release have not been studied in children less than 6 years of age, and NTP-METHYLPHENIDATE ER-C should not be used in this patient population. There are no data available for the use of methylphenidate hydrochloride extended release in patients over 65 years of age.

Hepatic Insufficiency: Methylphenidate hydrochloride extended release has not been studied in patients with hepatic insufficiency.

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 metabolic product, PPAA, is predominantly (80%) cleared through the urine.

STORAGE AND STABILITY
Store at controlled room temperature (15-30ºC). Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

NTP-METHYLPHENIDATE ER-C Extended-release Tablets contain methylphenidate hydrochloride as the medicinal ingredient and are available in 18 mg, 27 mg, 36 mg and 54 mg dosage strengths. The 18 mg capsule-shaped, film-coated, extended release tablets are yellow and engraved with **N** on one side and **18** on the other side. The 27 mg capsule-shaped, film-coated, extended release tablets are grey and printed with **N** on one side and **27** on the other side. The 36 mg capsule-shaped, film-coated, extended release tablets are white to off-white and printed with **N** on one side and **36** on the other side. The 54 mg capsule-shaped, film-coated, extended release tablets are brownish-red and engraved with **N** on one side and **54** on the other side. All dosage strengths are supplied in bottles containing 100 and 500 tablets. In clinical studies, a dose of 72 mg was achieved by taking two 36 mg tablets. There is no 72 mg tablet available.

Composition

NTP-METHYLPHENIDATE ER-C contains the following non-medicinal ingredients: hydroxypropyl methylcellulose, lactose monohydrate, microcrystalline cellulose, polyvinyl alcohol- polyethylene glycol copolymer and colloidal silica, simethicone and stearic acid.

Colourants present in the tablets are:

18 mg: D&C Yellow #10 aluminum lake, FD&C Red #40 aluminum lake, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

27 mg: iron oxide black, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

36 mg: polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

54 mg: hydroxpropyl methylcellulose, iron oxide yellow, iron oxide red, polyethylene glycol and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

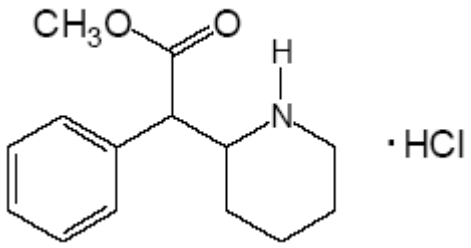
Drug Substance

Proper name: methylphenidate hydrochloride USP

Chemical name: Methyl-α-phenyl-2-piperidineacetate hydrochloride, (R*, R*)-(±)

Molecular formula and molecular mass: $C_{14}H_{19}NO_2$ •HCl 269.8

Structural formula:



Physicochemical properties: methylphenidate hydrochloride USP is a white crystalline powder

pH: methylphenidate hydrochloride solutions are acidic to litmus

pKa: 8.8

Solubility: freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone

Melting Point: 224˚C to 226˚C

CLINICAL TRIALS

Bioavailability Study

A randomized, single-dose, three-period, three-treatment crossover comparative bioavailability study of NTP-Methylphenidate ER-C 54 mg tablets (NTPharma Limited, Canada) and Concerta™ 54 mg ER tablets (Janssen-Ortho Inc., Canada) was conducted in 24 healthy adult male and female subjects. A summary of the comparative bioavailability data assessed under fed conditions is tabulated below:

Methylphenidate (1 x 54 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUCt (ng*h/mL)	170.440 179.811 (36)	161.974 171.358 (37)	105.23	100.80 – 109.85
AUC_{24} (ng*h/mL)	169.103 178.084 (35)	160.552 169.435 (36)	105.33	100.95 – 109.90
AUC_{inf} (ng*h/mL)	175.125 184.403 (35)	166.194 175.562 (36)	105.37	101.06 – 109.87
C_{max} (ng/mL)	18.719 19.433 (29)	15.878 16.709 (36)	117.90	110.17 – 126.17
T_{max}§ (h)	4.61 (21)	7.58 (26)		
$T_{½}$§ (h)	4.02 (25)	3.70 (18)		

* NTP-Methylphenidate ER-C 54mg tablets (NTPhrama Limited, Canada)

† Concerta™ 54mg ER tablets (Janssen-Ortho Inc., Canada, purchased in Canada)

§ Expressed as the arithmetic mean (CV%) only

A randomized, single-dose, two-period, two-treatment crossover comparative bioavailability study of NTP-Methylphenidate ER-C 54 mg tablets(NTPharma Limited, Canada) and Concerta™ 54 mg ER tablets (Janssen-Ortho Inc., Canada) was conducted in 25 healthy adult male and female subjects. A summary of the comparative bioavailability data assessed under fasting conditions is tabulated below:

Methylphenidate (1 x 54 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUCt (ng*h/mL)	131.848 139.785 (38)	132.231 139.495 (36)	99.71	94.87 – 104.80
AUC_{inf} (ng*h/mL)	137.782 145.888 (37)	137.795 145.774 (35)	99.99	95.27 – 104.94
C_{max} (ng/mL)	15.308 15.946 (31)	13.903 14.452 (29)	110.10	104.22 – 116.32
T_{max}§ (h)	3.81 (28)	7.20 (22)		
$T_{½}$§ (h)	5.13 (22)	3.98 (25)		

* NTP-Methylphenidate ER-C 54mg tablets (NTPharma Limited, Canada)

† Concerta™ 54mg ER tablets (Janssen-Ortho Inc., Canada, purchased in Canada)

§ Expressed as the arithmetic mean (CV%) only

Methylphenidate hydrochloride extended release was demonstrated to be effective in the treatment of ADHD in five randomized, double-blind, placebo-controlled studies in children, adolescents and adults who met the Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD.

Study Demographics and Designs

Table 2.1: Demographics and Designs for Controlled Clinical Trials in Patients with ADHD					
Study	**Design**	**Methylphenidate Hydrochloride Extended Release** **Dose/Treatment Duration**	**# of Patients**	**Mean Age** **(years) [Range]**	**Primary Efficacy Variable**
Controlled Studies in Children					
Study 1	Double-blind, randomized, 3-period, 6-sequence crossover, placebo-controlled, comparative vs. IR methylphenidate	18, 36 or 54 mg once daily	64	9.2 [6-12]	IOWA Conners Rating scale for inattention/ overactivity
Study 2	Double-blind, randomized, placebo-controlled, active-controlled, crossover, comparative vs. IR methylphenidate	18, 36 or 54 mg once daily	70	9.1 [6-12]	IOWA Conners Rating scale for inattention/ overactivity
Study 3	Double-blind, randomized, placebo-controlled, active-controlled, parallel group vs. IR methylphenidate	18, 36 or 54 mg once daily	282	8.7 [6-12]	IOWA Conners Rating scale for inattention/ overactivity
Controlled Studies in Adolescents					
Study 4	Double-blind, randomized, placebo-controlled	titration to 72 mg once daily	220	14.7 [13-18]	Investigator ADHD rating scale
Controlled Studies in Adults					
Study 5	Double-blind, randomized, placebo-controlled, parallel group, dose-response	fixed doses of 18, 36 and 72 mg once daily	401	34.0 [18-63]	Investigator-rated Connors Adult ADHD Rating Scale (CAARS) total score

Children

Three double-blind, active- and placebo-controlled studies were conducted in 416 children aged six to twelve. The controlled studies compared methylphenidate hydrochloride extended release q.d. (18, 36 or 54 mg), methylphenidate hydrochloride t.i.d. over 12 hours (15, 30 or 45 mg total daily dose), and placebo in two single-centre, 3-week, crossover studies (Study 1 and Study 2) and in a multicentre, 4-week, parallel-group comparison (Study 3). The primary comparison of interest in all three trials was methylphenidate hydrochloride extended release versus placebo.

Symptoms of ADHD were evaluated by community school teachers using the Inattention/Overactivity with Aggression (IOWA) Conners scale. Significant reduction in the Inattention/Overactivity subscale in the treatment group versus the placebo was shown consistently across all three controlled studies for methylphenidate hydrochloride extended release q.d. and methylphenidate hydrochloride t.i.d. ($p < 0.001$). The scores for the placebo-controlled parallel study for all three treatment groups are presented in Figure 2.1.

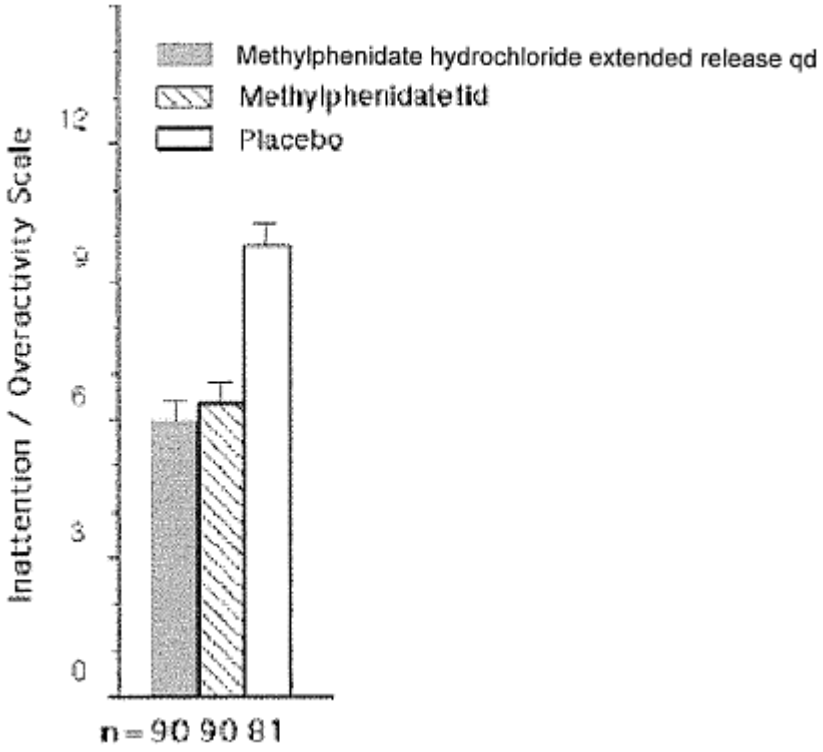


Figure 2.1: **Mean community school teacher IOWA Conners Inattention/Overactivity scores with methylphenidate hydrochloride extended release q.d. (18, 36 or 54 mg), methylphenidate hydrochloride t.i.d. over 12 hours (15, 30 or 45 mg total daily dose), and placebo. The study involved 4 weeks of parallel-group treatments with a Last Observation Carried Forward analysis for weeks 2 to 4. Data at Week 4 is shown. Error bars represent mean plus standard error of the mean.**

In the two placebo-controlled crossover studies (Studies 1 and 2), symptoms of ADHD were evaluated by laboratory school teachers using the SKAMP (Swanson, Kotkin, Agler, M-Flynn and Pelham) laboratory school rating scale. Significant improvement in attention and behaviour versus placebo was shown consistently across the two studies ($p < 0.005$). Efficacy was maintained through 12 hours after dosing, and the sustained beneficial effects of methylphenidate hydrochloride extended release q.d. therapy seen throughout the laboratory classroom day were comparable in duration to those with methylphenidate hydrochloride t.i.d. Figure 2.2 presents the laboratory school teacher SKAMP ratings for methylphenidate hydrochloride extended release q.d., methylphenidate hydrochloride t.i.d. and placebo in Study 1. Similar results were obtained in Study 2.

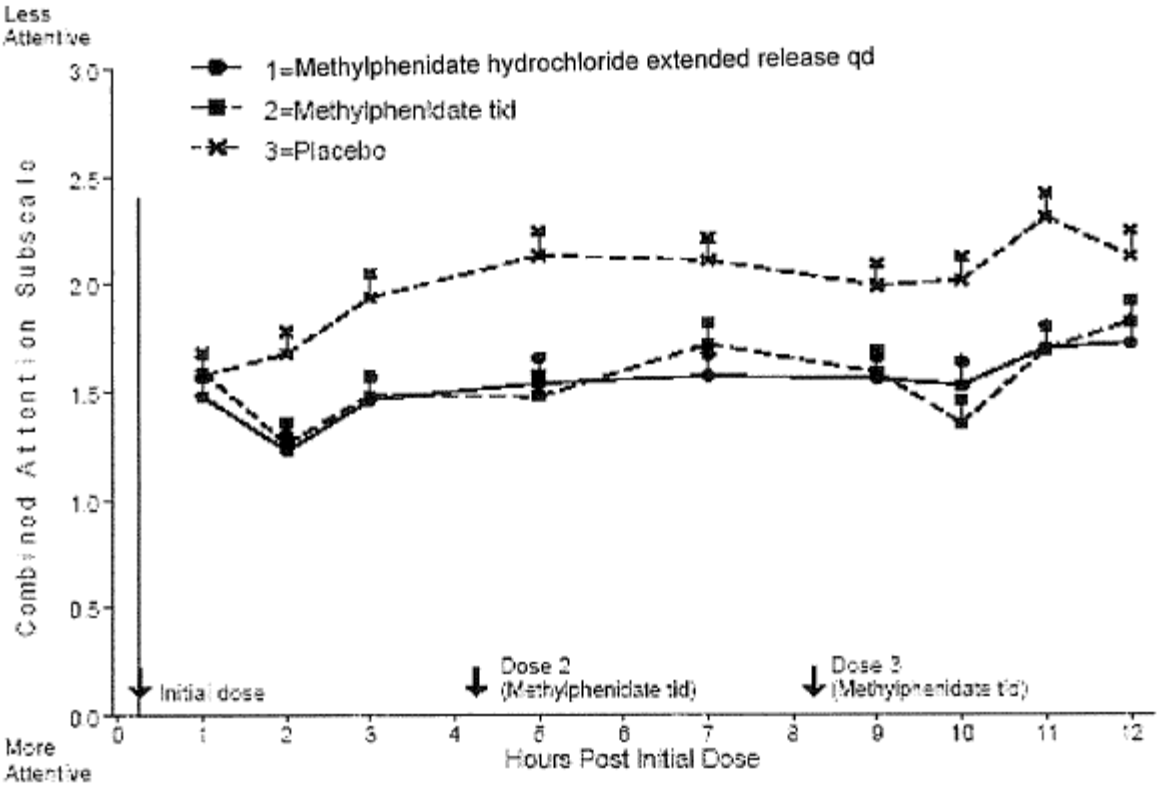


Figure 2.2: **Mean laboratory school teacher SKAMP Ratings of Combined Attention (Study 1) with methylphenidate hydrochloride extended release q.d. (18, 36 or 54 mg), methylphenidate hydrochloride t.i.d. over 12 hours (15, 30 or 45 mg total daily dose) and placebo. Error bars represent mean plus standard error of the mean. The sample sizes for methylphenidate hydrochloride extended release, methylphenidate hydrochloride t.i.d., and placebo groups were 60, 62 and 60, respectively.**

Adolescents

In a randomized, double-blind, multicentre, placebo-controlled trial (Study 4) involving 177 patients, methylphenidate hydrochloride extended release was demonstrated to be effective in the treatment of ADHD and was well tolerated in adolescents aged 13 to 18 at doses up to 72 mg/day (1.4 mg/kg/day). Of 220 patients who entered an open 4-week titration phase, 177 were titrated to an individualized dose (maximum 72 mg/day) based on meeting specific improvement criteria on the ADHD Rating Scale and the Global Assessment of Effectiveness with acceptable tolerability. Patients who met these criteria were then randomized to receive either their individualized dose of methylphenidate hydrochloride extended release (18 - 72 mg/day, n = 87) or placebo (n = 90) during a two-week double-blind phase. At the end of this phase, mean scores for the investigator rating on the ADHD Rating Scale for methylphenidate hydrochloride extended release were significantly improved relative to placebo (CON –14.93; PLA –9.58; p=0.001). Mean scores for methylphenidate hydrochloride extended release and placebo, respectively, at the end of the double-blind phase were 16.62 and 21.40, compared to 31.55 and 30.99 at baseline.

Adults

A 5-week, randomized, double-blind, multicentre, placebo-controlled, dose-response trial (Study

5) was conducted in 401 adults with ADHD aged 18 to 65 years using fixed once daily methylphenidate hydrochloride extended release doses of 18 mg, 36 mg and 72 mg. Efficacy was evaluated by the mean change from baseline to double-blind endpoint in the investigator-rated Connors' Adult ADHD Rating Scale (CAARS) total score. All doses of methylphenidate hydrochloride extended release (18 mg, 36 mg and 72 mg/day) were statistically significantly superior to placebo in improving the CAARS total scores at double-blind endpoint compared to baseline (mean change of -7.6 for placebo, -10.6 ($p=0.0146$) for methylphenidate hydrochloride extended release 18 mg, -11.5 ($p=0.0131$) for methylphenidate hydrochloride extended release 36 mg and -13.7 ($p<0.0001$) for the methylphenidate hydrochloride extended release 72 mg). Statistically significant differences compared to placebo were first observed at Week 1. Secondary endpoints included the investigator-rated Clinical Global Impressions - Severity (CGI-S) and the CAARS-S:S (patient-rated CAARS scale). The results from the secondary endpoints were consistent with the primary endpoint.

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

Methylphenidate hydrochloride is a sympathomimetic agent classified as a central nervous system (CNS) stimulant. Its mechanism of action is not entirely understood; however, it blocks the reuptake and enhances the release of dopamine and norepinephrine in the mammalian brain, an effect that increases dopamine and norepinephrine levels in the synaptic cleft. In vitro radioligand binding studies demonstrate that binding of methylphenidate in the brain is localized to dopamine-rich areas. Methylphenidate releases dopamine from a reserpine-sensitive storage pool and inhibits the catecholamine metabolic enzyme, monoamine oxidase (MAO), in the brain of rats.

Methylphenidate is a racemic mixture comprised of the *d*- and *l*-threo stereoisomers. The *d*-isomer is pharmacologically active; the *l*-isomer has little pharmacologic activity. In a number of animal models, methylphenidate enhances locomotor activity and induces stereotypic behaviours. Recent clinical findings in ADHD children suggest an abnormality in the dopamine transporter gene (DAT_1), the D_4 receptor gene (DRD-4) and/or the D_2 receptor gene that may be at least partly overcome by the dopaminergic effects of methylphenidate, suggesting a possible mode of action.

Safety Pharmacology

Methylphenidate hydrochloride had no effect in hERG-transfected cells or on the action potential of guinea pig papillary muscles. The no observed adverse effect level (NOAEL) for stimulatory effects on the cardiovascular system in conscious dogs (increased blood pressure and heart rate) was 10 mg/kg. The NOAEL for stimulatory effects on the respiratory system in free-moving rats was 3 mg/kg. The NOAEL for methylphenidate hydrochloride's convulsion evoking action in mice was 10 mg/kg.

Pharmacokinetics

Studies primarily in humans and rats, as well as limited information available for mice, dogs, monkeys and other species, demonstrate that methylphenidate is readily absorbed, distributed, metabolized and eliminated regardless of the route of administration. While the kinetic rates for these processes are similar among different species, there are differences in metabolic profiles. Distribution of metabolites differs from that of the unchanged parent material, with most of the material that reaches the brain consisting of the unchanged parent compound. Biotransformation in the gut or first-pass metabolism, or both, is common among the species studied. The primary metabolite in humans and a major metabolite in other species is alpha-phenyl-alpha-(2-piperidyl) acetic acid (PPAA), also commonly called ritalinic acid. Pharmacokinetic data showed dose-dependent exposure to methylphenidate and PPAA in adult animals; in juvenile rats, exposure was more than dose-proportional. In the presence of alcohol, an intermediate metabolite, ethylphenidate, is produced. The amount of ethylphenidate production is proportional to the blood alcohol concentration. Excretion of radioactivity into breast milk was observed after single oral administration of 5 mg/kg ^{14}C-methylphenidate hydrochloride to lactating rats.

TOXICOLOGY

The toxicology program for methylphenidate and the oral controlled-release OROS methylphenidate dosage form consists of acute toxicity, long-term toxicity, carcinogenicity and mutagenicity, reproductive and developmental toxicity, and other special toxicity studies.

Acute Toxicity

The acute toxicity of methylphenidate hydrochloride has been studied primarily in mice and rats, and additionally in rabbits and dogs. Published oral LD_{50} values for rodents and rabbits range from approximately 190 to 900 mg/kg. The probable cause of death in LD_{50} studies was excessive central adrenergic stimulation. Clinical signs noted with high doses of methylphenidate in animal acute toxicity studies include agitation and increased motor activity, tremors and convulsions, decreased food consumption and stereotypic behaviours such as licking or gnawing.

A dog study was conducted to study the abuse potential of methylphenidate hydrochloride extended release (N=8) and immediate release methylphenidate (N=8). The dogs were intravenously administered with pulverized methylphenidate hydrochloride extended release or methylphenidate tablets mixed with liquid. Death occurred after a single 0.5 mg or 1 mg/kg dose of methylphenidate hydrochloride extended release. Mortality was not observed in methylphenidate-treated dogs dosed at 1 mg/kg/day for 2 weeks. It is likely that the deaths were due the particles present in the pulverized methylphenidate hydrochloride extended release tablets.

Long-Term Toxicity

Treatment with methylphenidate hydrochloride at repeated high doses has demonstrated transient effects on body weight in rats and mice. The liver was the primary target organ for toxicity in mice and rats, with male mice being the most sensitive showing hepatocellular degeneration. Methylphenidate has shown some effects on maturation and oestrous cyclicity in neonatal rats; oestrous cycles were reversibly affected in older rats. Reversible effects of methylphenidate were seen on skeletal growth in neonatal rats; such effects were not seen in older rats. Endocrine

effects of MPH have generally been inconsistent or did not show a dose response. The potential gastrointestinal (GI) effects and systemic toxicity of the OROS methylphenidate dosage form were evaluated in a study conducted in dogs. Except for excessive salivation, no other treatment-related clinical signs were observed. No treatment-related findings were seen in body or organ weights, physical exams, ophthalmic exams, qualitative food consumption, hematology, clinical chemistry, urinalysis, macroscopic exams or histopathologic evaluation of tissues. No treatment-related GI irritation or systemic effects were seen for oral doses up to 72 mg/day for 30 days.

A second study in beagle dogs was conducted to determine the possible local gastrointestinal and systemic effects of methylphenidate hydrochloride extended release after daily administration (0, 72, 144 or 216 mg/day) for 4 weeks. Females in all methylphenidate hydrochloride extended release groups showed toxicologic effects such as hyperactivity, reduced food consumption, and decreased mean body weight gain; in males similar effects were seen only in the two higher methylphenidate hydrochloride extended release groups (144 and 216 mg/day). However, with the exception of mean body weight gain in 216 mg/day females, the methylphenidate hydrochloride extended release -related changes resolved during recovery.

Carcinogenicity and Mutagenicity

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate hydrochloride caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of methylphenidate hydrochloride extended release on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumour type. There was no increase in total malignant hepatic tumours. The mouse strain used is sensitive to the development of hepatic tumours, and the significance of these results to humans is unknown.

Methylphenidate hydrochloride did not cause any increases in tumours in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of methylphenidate hydrochloride extended release on a mg/kg and mg/m^2 basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate hydrochloride.

Methylphenidate was not mutagenic in the in vitro Ames reverse mutation assay or the in vitro mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an in vitro assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative in vivo in males and females in the mouse bone marrow micronucleus assay.

Reproductive and Developmental Toxicity

Studies have been conducted in mice, rats and rabbits to evaluate the potential reproductive and developmental toxicity of methylphenidate. Rats appear to be a better animal model than rabbits for developmental/reproductive studies of methylphenidate, based on plasma AUC ratios of drug:metabolite.

Reproductive toxicity was studied using a Reproductive Assessment by Continuous Breeding (RACB) protocol or Sperm Morphology Vaginal Cytology Evaluations (SMVCE) endpoints to assess male and female reproductive functions. Methylphenidate hydrochloride did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of methylphenidate hydrochloride extended release on a mg/kg and mg/m^2 basis, respectively. A perinatal and postnatal development study with neurobehavioural assessments in rats indicated slight developmental delay and marginal alterations in neuromotor performance in offspring of the high-dose dams treated with 30 mg/kg/day methylphenidate hydrochloride (approximately 15 and 3 times the maximum recommended daily human dose for methylphenidate hydrochloride extended release tablets [54 mg methylphenidate hydrochloride] on a mg/kg and mg/m^2 basis, respectively). No effects on learning and memory were seen in offspring and no adverse effects were noted in offspring of dams treated with methylphenidate hydrochloride doses of 12.5 mg/kg/ day and lower. A teratology study conducted in rats supports the conclusion that methylphenidate is not a developmental toxicant at the dose levels tested, up to 30 mg/kg/ day. The maternal no-observed-adverse-effect level (NOAEL) of methylphenidate hydrochloride was 5 mg/kg/ day. No adverse effects on embryo/fetal viability, growth or malformations were seen. The developmental toxicity NOAEL of methylphenidate hydrochloride was at least 30 mg/kg/ day. In a study conducted in rabbits, methylphenidate hydrochloride was shown to have teratogenic effects when given in doses of 200 mg/kg/ day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

Weaning juvenile rats (F_0) of both sexes were administered methylphenidate hydrochloride at total daily doses of 5, 12.5, and 30 mg/kg for approximately 4.5 months. The no observed adverse effect level (NOAEL) for F_0 juvenile toxicity was considered to be 12.5 mg/kg/day for males and 30 mg/kg/day for females. For F_1 developmental toxicity the NOAEL was considered to be 12.5 mg/kg/day.

Other Special Toxicity Studies

Five system transit and drug release studies conducted with the OROS methylphenidate dosage form in dogs showed no unexpected clinical signs during transit through the gastrointestinal (GI) tract. Membrane shells remained intact during GI transit with cumulative release of active ingredient generally comparable in vitro and in vivo.

Cellular toxicity profile of methylphenidate and effects of methylphenidate on mitochondrial function were evaluated in vitro using an MTT(3-[4,5-dimethythiazole-2-yl]-2,5-di-phenyl-tetrazolium bromide) assay. Results demonstrated that MPH in cell culture medium, at approximate concentrations of 0.125 and 0.25 mg/mL, was noncytotoxic to L-929 mouse fibroblast cells.

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PART III: CONSUMER INFORMATION

C

NTP-METHYLPHENIDATE ER-C
methylphenidate hydrochloride
Extended-release Tablets

This leaflet is part III of a three-part "Product Monograph" published when NTP-METHYLPHENIDATE ER-C was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NTP-METHYLPHENIDATE ER-C. Contact your doctor or pharmacist if you have any questions about the drug.

This information is for patients taking NTP-METHYLPHENIDATE ER-C Extended-release Tablets for the treatment of Attention Deficit Hyperactivity Disorder, or their parents or caregivers.

Please read this before you / your child start taking NTP-METHYLPHENIDATE ER-C tablets. Remember, this information does not take the place of your doctor's instructions.

The following have been reported with use of NTP-METHYLPHENIDATE ER-C and other stimulant medicines.

1. Heart-related problems:

- **sudden death in patients who have heart problems or heart defects**
- **stroke and heart attack in adults**
- **increased blood pressure and heart rate**

Tell your doctor if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your doctor may wish to check you or your child carefully for heart problems before starting NTP-METHYLPHENIDATE ER-C.

Your doctor may wish to check you or your child's blood pressure and heart rate regularly during treatment with NTP-METHYLPHENIDATE ER-C.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking NTP-METHYLPHENIDATE ER-C.

2. Mental (Psychiatric) problems:

All Patients

- **new or worse behavior and thought problems**
- **new or worse bipolar illness**
- **new or worse aggressive behavior or hostility**

Children and Teenagers

- **new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms**

Tell your doctor about any mental problems you or your child have, or about a family history of suicide, bipolar illness, or depression.

Call your doctor right away if you or your child have any new or worsening mental symptoms or problems while taking NTP-METHYLPHENIDATE ER-C, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

ABOUT THIS MEDICATION

What the medication is used for:

NTP-METHYLPHENIDATE ER-C is a once-a-day treatment for Attention Deficit Hyperactivity Disorder, or ADHD, in children 6 years of age or older, adolescents and adults. Methylphenidate hydrochloride is a central nervous system stimulant that has been used to treat ADHD for more than 30 years.

ADHD has three main types of symptoms: inattention, hyperactivity and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all three types of symptoms. Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis. Symptoms of ADHD in adults may include a lack of organization, problems starting tasks, impulsive actions, daydreaming, slow processing of

information, difficulty learning new things, irritability, lack of esteem and excessive effort to maintain some organization.

What it does:
Part of the NTP-METHYLPHENIDATE ER-C tablet dissolves right after you / your child swallow it in the morning, giving you / your child an initial dose of medication. The rest of the medication is slowly released during the day to keep improving the symptoms of ADHD. NTP-METHYLPHENIDATE ER-C helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

When it should not be used:
You / your child should NOT take NTP-METHYLPHENIDATE ER-C if you / your child:

- have significant anxiety, tension or agitation because NTP-METHYLPHENIDATE ER-C may make these conditions worse;
- are allergic to methylphenidate hydrochloride or any of the other ingredients in NTP-METHYLPHENIDATE ER-C;
- have glaucoma, an eye disease;
- have 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;
- have a family history of motion tics, verbal tics or Tourette's syndrome;
- have symptomatic cardiovascular disease;
- have moderate to severe high blood pressure;
- have advanced arteriosclerosis (hardened arteries);
- have hyperthyroidism (an overactive thyroid gland); or are taking monoamine oxidase inhibitors (a type of drug, see INTERACTIONS WITH THIS MEDICATION).

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

What the medicinal ingredient is:
methylphenidate hydrochloride

What the nonmedicinal ingredients are:
NTP-METHYLPHENIDATE ER-C contains the following non-medicinal ingredients: hydroxypropyl methylcellulose, lactose monohydrate, microcrystalline cellulose, polyvinyl alcohol-polyethylene glycol copolymer and colloidal silica, simethicone and stearic acid.

Colourants present in the tablets are:

18 mg: D&C Yellow #10 aluminum lake, FD&C Red #40 aluminum lake, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

27 mg: iron oxide black, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

36 mg: polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

54 mg: hydroxpropyl methylcellulose, iron oxide yellow, iron oxide red, polyethylene glycol and titanium dioxide.

What dosage forms it comes in:
extended-release tablets: 18 mg, 27 mg, 36 mg and 54 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Drug Dependence
Abuse of NTP-METHYLPHENIDATE ER-C 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. NTP-METHYLPHENIDATE ER-C generally should not be used in children, adolescents or adults with known structural heart abnormalities.

BEFORE you use NTP-METHYLPHENIDATE ER-C, talk to your doctor or pharmacist if you / your child:

- have structural heart abnormalities;
- have mental problems, including psychosis, mania, bipolar illness, or depression;
- have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms);
- have mild high blood pressure;
- have a narrowing or blockage of your gastrointestinal tract (your oesophagus, stomach, or small or large intestine);

- have a family history of sudden death or death related to heart problems;
- do strenuous exercise;
- take other drugs for ADHD; or
- have or have had any disorder of the blood vessels in the brain (e.g. aneurysm, stroke, vasculitis).

Tell your doctor ***immediately*** if you / your child develop any of the above conditions or symptoms while taking NTP-METHYLPHENIDATE ER-C. He/she will decide if you can start/continue taking NTP-METHYLPHENIDATE ER-C.

BEFORE taking NTP-METHYLPHENIDATE ER-C, tell your doctor if you are pregnant or plan to become pregnant.

Tell your doctor if you are nursing a baby. If you take NTP-METHYLPHENIDATE ER-C, it may be in your breast milk.

Your doctor will monitor your progress with NTP-METHYLPHENIDATE ER-C and may require you to do occasional tests to ensure your health and safety.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about ***all*** medicines that you / your child are taking. Your doctor should decide whether you / your child can take NTP-METHYLPHENIDATE ER-C with other medicines. These include:

- clonidine;
- other medicines that a doctor has prescribed;
- medicines that you buy yourself without a prescription;
- any herbal remedies that you /your child may be taking.

You / your child should not take NTP-METHYLPHENIDATE ER-C with monoamine oxidase (MAO) inhibitors.

While on NTP-METHYLPHENIDATE ER-C, do not start taking a new medicine or herbal remedy before checking with your doctor.

You should avoid alcoholic drinks while taking NTP-METHYLPHENIDATE ER-C.

NTP-METHYLPHENIDATE ER-C may change the way your / your child's body reacts to certain medicines. These include medicines used to treat depression (e.g., amitriptyline, imipramine and fluoxetine), prevent seizures (e.g., phenobarbitone, phenytoin, carbamazepine and primidone) or prevent blood clots (commonly called "blood thinners", e.g., warfarin).

Your doctor may need to change your / your child's dose of these medicines if you / your child are taking them with NTP-METHYLPHENIDATE ER-C.

PROPER USE OF THIS MEDICATION

Do not chew, crush or divide the tablets. Swallow NTP-METHYLPHENIDATE ER-C tablets whole with water or other liquids, such as milk or juice.

Take NTP-METHYLPHENIDATE ER-C once each day in the morning with or without food.

NTP-METHYLPHENIDATE ER-C has not been studied and should not be used in children under six years of age. Methylphenidate hydrochloride extended release has not been studied in adults over 65 years of age.

NTP-METHYLPHENIDATE ER-C may be a part of your / your child's overall treatment for ADHD. Your doctor may also recommend that you / your child have counselling or other therapy.

As with all medicines, never share NTP-METHYLPHENIDATE ER-C with anyone else.

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

Overdose:

In the event of overdosage, contact your doctor hospital emergency department or regional Poison Control Centre.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In the clinical studies with patients using methylphenidate extended release, the most common side effects were headache, stomach pain, sleeplessness, dry mouth, nausea (feeling sick) and decreased appetite. Other side effects seen with methylphenidate extended release, include vomiting, dizziness, nervousness, tics, allergic reactions, increased blood pressure, and abnormal thinking or hallucinations.

Tell your doctor if you / your child have blurred vision when taking NTP-METHYLPHENIDATE ER-C.

Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate hydrochloride in children. Your doctor will be carefully watching your child's height and weight. If you / your child are not growing or gaining weight as your doctor expects, your doctor may stop you / your child's NTP-METHYLPHENIDATE ER-C treatment.

Stimulants may impair your / your child's ability to operate potentially hazardous machinery or vehicles. You should exercise caution until you are reasonably certain that NTP-METHYLPHENIDATE ER-C does not adversely affect your / your child's ability to engage in such activities.
This is not a complete list of side effects. For any unexpected effects while taking NTP-METHYLPHENIDATE ER-C, contact your doctor or pharmacist.

HOW TO STORE IT

NTP-METHYLPHENIDATE ER-C should be stored in a safe place at room temperature (between 15-30ºC). Do not store this medicine in hot, damp or humid places.

Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting NT Pharma Canada at:

1-800-268-4127 ext. 5005 (English);
1-877-777-9117 (French)
or druginfo@NT Pharma.com

Please consult your doctor or pharmacist with any questions or concerns you may have regarding your individual condition.

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