

PRODUCT MONOGRAPH

 **Biphentin[®]**

**Methylphenidate Hydrochloride Controlled Release Capsules
10, 15, 20, 30, 40, 50, 60 and 80 mg**

Central Nervous System Stimulant

Purdue Pharma
575 Granite Court
Pickering, ON
L1W 3W8

Control No.: 123442

DATE OF REVISION:
June 19, 2009

PRODUCT MONOGRAPH

NAME OF DRUG

◇ **Biphentin**[®]

Methylphenidate Hydrochloride Controlled Release Capsules

10, 15, 20, 30, 40, 50, 60 and 80 mg

THERAPEUTIC CLASSIFICATION

Central Nervous System Stimulant

ACTIONS

Methylphenidate is a central nervous system (CNS) stimulant. The mode of action of stimulants in Attention-Deficit Hyperactivity Disorder (ADHD) is not completely understood, but they are thought to act primarily through indirect mechanisms, such as release of dopamine and norepinephrine from neuronal pools, and inhibition of neurotransmitter reuptake.

There is some evidence suggesting that the mechanism whereby methylphenidate produces its mental and behavioural effects in children is related to a dose-dependent blockade of the dopamine transporter and an increase in extracellular dopamine. While the evidence regarding how these effects relate to the condition of the CNS is not conclusive, it is likely that an increase in dopamine transporter activity is part of the underlying mechanistic basis of ADHD.

Pharmacokinetics of Methylphenidate:

Methylphenidate is rapidly and extensively absorbed following oral administration - with peak blood levels obtained in 1 to 3 hours.

Methylphenidate is excreted almost entirely in the urine. The primary route of metabolism for methylphenidate is deesterification to the inactive metabolite ritalinic acid (α -phenyl-2-piperidine acetic acid), which represents 60-81% of the administered dose, and 6-oxy- α -phenyl-2-piperidine acetic acid (9-12% of the administered dose). Unchanged drug accounts for less than 1% of the administered dose. First pass metabolism results in an absolute bioavailability of 30% with large inter-individual differences (11-52%).

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

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

Pharmacokinetics and Pharmacodynamics of Biphentin:

In a single dose study in healthy adult volunteer subjects, **Biphentin[®]** (methylphenidate hydrochloride controlled release capsules, 20 mg) was fully bioavailable, relative to two separate 10 mg doses of an immediate-release reference formulation (Ritalin[®]), under both fasted and fed conditions (relative AUC_t 96% and 107%, respectively). In a single dose study in young children (6 - 12 years) with ADHD, **Biphentin**, when given at a dose equal to the patient's pre-study methylphenidate dose (mean dose 38.6 mg), following a child's typical breakfast, was fully bioavailable relative to the same daily dose of immediate-release methylphenidate (Ritalin[®]) given as two separate doses (relative AUC_t 101%).

Biphentin was designed to be an alternative to separate doses of immediate release methylphenidate by providing a biphasic plasma concentration time profile when given as a single dose. The rate of increase in plasma methylphenidate concentration with the controlled release formulation was similar to that with the immediate-release formulation. In adults the initial peak concentration occurred at 1.7 hours post-dose for **Biphentin** and at 1.8 hours post-dose for the immediate-release formulation, when given under fasting conditions, and at 2.0 hours post-dose and 2.5 hours post-dose, respectively, when given with food. The initial maximum concentration (C_{max}) achieved with the controlled release formulation was 76% (fasted) and 84% (fed) of that of immediate-release methylphenidate. In young children, being

treated for ADHD with methylphenidate, the initial peak concentration occurred at 2.6 hours post-dose for Biphentin and at 2.1 hours post-dose for the immediate-release formulation, when given at doses equal to the children's pre-study maintenance doses. The initial maximum concentration achieved with the controlled release formulation was 79% of that of immediate-release methylphenidate.

A double-blind, placebo-controlled, crossover comparison of the pharmacodynamics of **Biphentin** and immediate-release methylphenidate in children (age 6 to 17 years) with ADHD demonstrated equivalent improvements on the same daily dose, with a similar time-course, on both behavioural and cognitive parameters, relative to placebo. **Biphentin** was given as a single morning dose while immediate-release methylphenidate was given at the same daily dose, in equally divided doses in the morning and at lunchtime. Improvements relative to placebo were noted within 1 hour on Biphentin and persisted into the early evening.

INDICATIONS

Biphentin® (methylphenidate hydrochloride controlled release capsules) is indicated for treatment of Attention-Deficit Hyperactivity Disorder (ADHD) in:

- **Children (6-11 years of age)**
- **Adolescents (12-18 years of age)**
- **Adults (> 18 years of age)**

Children (<6 years of age)

Biphentin should not be used in children under 6 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 two or more settings, e.g. school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least 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

Biphentin 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 will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Long-Term Use

The effectiveness of **Biphentin** for long-term use, i.e. for more than 4 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use **Biphentin** 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 hydrochloride or to any other ingredient in the formulation or component of the container. For a complete listing of excipients, see the **PHARMACEUTICAL INFORMATION**, Non-medicinal Ingredients (all strengths) section of this 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 **PRECAUTIONS**; **Drug Interactions**).

WARNINGS**Serious Warnings and Precautions**

- **Drug Dependence** (see **Dependence/Tolerance** section below)

General

Biphentin[®] (methylphenidate hydrochloride controlled release capsules) has not been compared to other controlled release methylphenidate preparations on the Canadian market, and therefore is not interchangeable.

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 adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: a) are involved in strenuous exercise or activities, b) use other stimulants, or c) have a family history of sudden/cardiac death.

Prior to the initiation of treatment, a personal and family history (including assessment for a family history 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 judgement, 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.

Cardiovascular

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, **Biphentin** generally should not be used in children or adolescents with known serious 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 death, 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.

Pre-existing Cardiovascular and Cerebral Vascular Conditions

CNS stimulants should be used with caution in patients with a condition of the cardiovascular or cerebrovascular system, 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 stimulants and monitored for new conditions of the heart or brain during the course of treatment.

Hypertension

Hypertension may occur during methylphenidate treatment in some patients. Caution is particularly indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction or hyperthyroidism.

Blood pressure should be monitored at appropriate intervals in patients receiving stimulants, especially in patients with pre-existing conditions that may result in hypertension.

Drug Dependence/Tolerance

Biphentin 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.

Chronic abuse can lead to marked tolerance and psychological 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 and underlying hyperactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

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.

Psychiatric

Depression and Psychotic Disorders

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

Fatigue

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

Neurologic**Seizures**

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in the absence of seizures and, very rarely, in patients with no prior EEG evidence or history of seizures. Clinical experience has shown that a small number of patients may experience an increase in seizure frequency when treated with methylphenidate. If seizure frequency rises, the drug should be discontinued.

Ophthalmologic**Visual Disturbance**

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

Use in Pregnancy and Lactation

Studies to establish safe use of methylphenidate in pregnant women have not been conducted. Therefore, **Biphentin** should not be given to pregnant women unless the potential benefit outweighs the risk to the fetus.

It is not known whether methylphenidate and/or its metabolites pass into breast milk. For safety reasons, the physician should assess the patient's medical condition and advise on the following options: refrain from breast-feeding infants while taking **Biphentin**, or discontinue the drug while nursing.

Pediatrics (< 6 years of age)

Biphentin 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; Endocrine and Metabolism**).

PRECAUTIONS

Drug treatment is not indicated in all cases of Attention Deficit Hyperactivity Disorder and should be considered only in light of the complete history and evaluation. The decision to prescribe **Biphentin®** (methylphenidate hydrochloride controlled release capsules) should depend on the physician's assessment of the chronicity and severity of the patient's symptoms and their appropriateness for his/her age. Treatment 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 methylphenidate is usually not indicated.

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

Patients with motor tics or with a family history or diagnosis of Tourette's syndrome may be at risk for exacerbation of these conditions, although available evidence does not support a direct association with stimulant therapy.

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.

Long-term effects of methylphenidate have not been well established.

Because methylphenidate may affect performance, patients should be cautious when driving or operating machinery.

Drug Interactions

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

Because of possible increases in blood pressure and heart rate, **Biphentin** should be used cautiously with drugs with similar pharmacological actions.

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 **Biphentin** (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.

ADVERSE REACTIONS

Adverse events in children (6-11 years of age) and adolescents (12-18 years of age) with ADHD were evaluated in two Canadian randomized controlled clinical trials of **Biphentin®** (methylphenidate hydrochloride controlled release capsules) in comparison with placebo and immediate release methylphenidate. **Tables 1** and **2** list all adverse events occurring at an incidence of 1% or more, from both studies, in children (6-11 years of age) and adolescents (12-18 years of age), whether considered by the clinical investigator to be related to the study drug or not.

Adverse events in adults with ADHD were evaluated in a Canadian randomized controlled trial in comparison with placebo. A summary of adverse events occurring at an incidence of 1% or more is given in **Table 3**, which includes all events, whether considered by the clinical investigator to be related to the study drug or not.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1: Adverse Events¹ Reported in Biphentin Clinical Trials in Children 6-11 Years of Age (≥1%)

	Biphentin % (n = 68)	IR Methylphenidate % (n = 68)
Body as a Whole		
Headache	11.8	8.8
Abdominal Pain	8.8	8.8
Flu Syndrome	5.9	7.4
Pain	2.9	1.5
Infection	2.9	2.9
Asthenia	1.5	2.9
Malaise	1.5	0.0
Photosensitivity Reaction	1.5	0.0
Chills	1.5	4.4
Fever	1.5	1.5
Allergic Reaction	1.5	0.0
Neoplasm (benign nasal polyp)	0.0	1.5
Cardiovascular		
Hypertension	1.5	0.0
Vasodilatation	1.5	0.0
Central Nervous System		
Insomnia	22.1	14.7
Somnolence	11.8	4.4
Nervousness	8.8	8.8
Depression	7.4	4.4
Apathy	7.4	4.4

Table 1: Adverse Events¹ Reported in Biphentin Clinical Trials in Children 6-11 Years of Age (≥1%)

	Biphentin % (n = 68)	IR Methylphenidate % (n = 68)
Emotional Lability	2.9	8.8
Obsessive Behaviour	2.9	2.9
Vocal Tics	2.9	0.0
Speech Disorder	2.9	1.5
Motor Tics	2.9	1.5
Rebound	4.4	1.5
Sleep Disorder	1.5	2.9
Dizziness	1.5	0.0
Anxiety	1.5	0.0
Euphoria	1.5	1.5
Stereotypies	1.5	0.0
Depersonalization	0.0	1.5
Agitation	0.0	1.5
Hallucinations	0.0	1.5
Hyperkinesia	0.0	1.5
Tremor	0.0	1.5
Digestive		
Anorexia	22.1	19.1
Nausea	5.9	2.9
Increased Appetite	2.9	0.0
Vomiting	2.9	1.5
Diarrhea	0.0	2.9
Respiratory		
Pharyngitis	2.9	2.9
Asthma	1.5	1.5
Cough Increased	1.5	5.9
Rhinitis	0.0	1.5
Bronchitis	0.0	1.5
Skin and Appendages		
Rash	5.9	2.9
Eczema	1.5	0.0
Skin Discolouration	1.5	0.0
Special Senses		
Abnormal Vision	1.5	0.0
Conjunctivitis	1.5	0.0
Corneal Lesion	1.5	0.0
Otitis Media	1.5	0.0

¹Events are listed regardless of the causality assessment by the clinical investigator.

There were no adverse events reported to have occurred in <1% of the children in the **Biphentin** clinical trials.

Table 2: Adverse Events¹ Reported in Biphentin Clinical Trials in Adolescents 12-18 Years of Age (≥ 1%)

	Biphentin % (n = 40)	IR Methylphenidate % (n = 40)
Body as a Whole		
Headache	25.0	22.5
Flu Syndrome	7.5	7.5
Abdominal Pain	5.0	10.0
Asthenia	2.5	2.5
Infection	0.0	2.5
Pain	0.0	2.5
Cardiovascular		
Palpitation	2.5	0.0
Tachycardia	0.0	2.5
Syncope	0.0	2.5
Central Nervous System		
Nervousness	27.5	25.0
Somnolence	15.0	7.5
Dizziness	7.5	10.0
Insomnia	7.5	12.5
Depersonalization	7.5	0.0
Depression	2.5	5.0
Emotional Lability	5.0	5.0
Sleep Disorder	2.5	2.5
Vocal Tics	2.5	2.5
Apathy	2.5	0.0
Obsessive Behaviour	2.5	0.0
Vertigo	2.5	2.5
Anxiety	0.0	2.5
Rebound	0.0	2.5
Neurosis	0.0	2.5
Digestive		
Anorexia	7.5	27.5
Nausea	5.0	5.0
Increased Appetite	5.0	12.5
Vomiting	2.5	2.5
Diarrhea	2.5	0.0
Metabolic and Nutrition		
Thirst	0.0	2.5
Musculo-Skeletal		
Arthralgia	2.5	2.5
Respiratory		
Pharyngitis	5.0	2.5
Cough Increased	0.0	5.0
Asthma	0.0	2.5
Sinusitis	0.0	2.5

Table 2: Adverse Events¹ Reported in Biphentin Clinical Trials in Adolescents 12-18 Years of Age (≥ 1%)

	Biphentin % (n = 40)	IR Methylphenidate % (n = 40)
Skin and Appendages		
Pruritus	0.0	2.5
Urogenital		
Dysmenorrhea	0.0	2.5

¹Events are listed regardless of the causality assessment by the clinical investigator.

There were no adverse events reported to have occurred in <1% of the adolescents in the **Biphentin** clinical trials.

Table 3: Adverse Events¹ Reported in Biphentin Clinical Trials in Adults (≥1%)

	Biphentin % (n = 50)	Placebo % (n = 50)
Body as a Whole		
Headache	28.0	24.0
Asthenia	8.0	10.0
Abdominal Pain	4.0	6.0
Fever	4.0	0.0
Pain	2.0	6.0
Chest Pain	2.0	2.0
Accidental Injury	2.0	0.0
Body Odour	2.0	0.0
Allergic Reaction	2.0	0.0
Chills	0.0	2.0
Hernia	0.0	2.0
Flu Syndrome	0.0	2.0
Infection	0.0	4.0
Cardiovascular		
Tachycardia	6.0	4.0
Palpitation	2.0	2.0
Peripheral Vascular Disease	2.0	0.0
Central Nervous System		
Nervousness	24.0	4.0
Insomnia	22.0	10.0
Anxiety	18.0	0.0
Dry Mouth	12.0	2.0
Emotional Lability	10.0	2.0
Depression	8.0	2.0
Agitation	6.0	4.0
Akathisia	6.0	0.0

Table 3: Adverse Events¹ Reported in Biphentin Clinical Trials in Adults (≥1%)

	Biphentin % (n = 50)	Placebo % (n = 50)
Dizziness	4.0	2.0
Hypertension	4.0	2.0
Abnormal Thinking	4.0	0.0
Somnolence	2.0	4.0
Depersonalization	2.0	2.0
Twitching	2.0	2.0
Confusion	2.0	0.0
Neurosis	2.0	0.0
Paresthesia	2.0	0.0
Vasodilatation	2.0	0.0
Personality Disorder	0.0	2.0
Rebound	0.0	2.0
Digestive		
Anorexia	26.0	6.0
Nausea	20.0	8.0
Dyspepsia	4.0	4.0
Nausea and Vomiting	2.0	0.0
Constipation	2.0	0.0
Vomiting	2.0	0.0
Diarrhea	0.0	6.0
Haemic and Lymphatic		
Ecchymosis	0.0	2.0
Metabolic and Nutrition		
Weight Loss	2.0	0.0
Musculoskeletal		
Arthralgia	2.0	2.0
Myalgia	0.0	2.0
Respiratory		
Rhinitis	4.0	0.0
Cough Increased	2.0	0.0
Pharyngitis	2.0	0.0
Epistaxis	0.0	2.0
Hiccough	0.0	2.0
Skin and Appendages		
Sweating	6.0	0.0
Special Senses		
Abnormal Vision	2.0	0.0
Ear Disorder	2.0	0.0

¹ Events are listed regardless of the causality assessment by the clinical investigator.

There were no adverse events reported to have occurred in <1% of the adults in the **Biphentin** clinical trial.

Abnormal Hematologic and Clinical Chemistry Findings

None

Adverse Events Reported 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; sudden cardiac death; 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 other methylphenidate products: instances of abnormal liver function, e.g., hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been 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.

SYMPTOMS AND TREATMENT OF OVERDOSE

Signs and symptoms of acute overdose, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: agitation, cardiac arrhythmias, confusion, convulsions (may be followed by coma), delirium, euphoria, flushing, hallucinations, headache, hyperpyrexia, hyperreflexia, hypertension, muscle twitching, mydriasis and dryness of mucus membranes, palpitations, sweating, tachycardia, tremors and vomiting.

Management consists of 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 overdose has not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Biphentin[®] (methylphenidate hydrochloride controlled release capsules) has not been compared to other controlled release methylphenidate preparations on the Canadian market, and therefore is not interchangeable.

Biphentin 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 Biphentin varies widely.

Biphentin 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**).

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 adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: a) are involved in strenuous exercise or activities, b) use other stimulants, or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment, 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 judgement, 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.

Particular care should be taken in patients with symptoms of a psychiatric illness as there is an increased risk of comorbid disorder symptoms during stimulant treatment for ADHD (see **WARNINGS**).

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

Caution should be exercised in prescribing concomitant drugs.

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

Biphentin capsules should be swallowed whole and must never be crushed or chewed. The contents may be sprinkled on these soft foods: apple sauce, ice cream or yogurt.

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

Biphentin should be periodically discontinued to assess the patient's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Children (6 Years and Over)

In patients not currently treated with methylphenidate, **Biphentin** should be initiated in low doses, as a single daily dose in the morning. Dosage should be individualized on the basis of factors such as age, body weight and individual response.

The usual initial dose should be 10-20 mg/day orally.

Patients currently receiving immediate-release formulations of methylphenidate may be converted to the same daily dose of **Biphentin**, as a single daily dose in the morning.

The total daily dose may be adjusted in weekly increments of 10mg/day up to a maximum of 60 mg/day. In some children, higher doses (maximum 1mg/kg/day) may be necessary and in such cases, careful monitoring for adverse events should be implemented.

If 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 the drug should be discontinued.

Adults

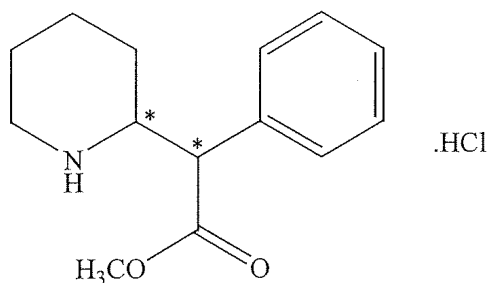
Biphentin is to be administered as a single daily dose in the morning. The usual initial dose should be 10-20 mg/day orally. The daily dose should be titrated weekly, in increments of 10 mg, according to individual response, up to a maximum dose of 80 mg/day.

PHARMACEUTICAL INFORMATION**Drug Substance**

Proper Name: Methylphenidate Hydrochloride

Chemical Name: α -phenyl-2-piperidine acetic acid methyl ester hydrochloride

Structural Formula:



Molecular Formula: C₁₄H₁₉NO₂HCl

Molecular Weight: 269.77

Description: Methylphenidate HCl is a white, odourless crystalline powder. Solutions are acidic to litmus.

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

pKa: 8.9

Melting Point: 224 - 226°C

Non-medicinal Ingredients (all strengths): gelatin*, hydroxypropyl methylcellulose, methyl acrylic acid copolymer, polyethylene glycol, sugar beads, talc, triethyl citrate

**Capsule Shells:*

- 10 mg: FD&C Blue No. 1, titanium dioxide
- 15 mg: D&C Red No.28, D&C Yellow No. 10, FD&C Red No. 40, titanium dioxide
- 20 mg: D&C Red No. 33, D&C Yellow No. 10, titanium dioxide
- 30 mg: FD&C Blue No. 1, FD&C Red No. 3, titanium dioxide
- 40 mg: D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, titanium dioxide
- 50 mg: D&C Yellow No. 10, FD&C Green No. 3, titanium dioxide
- 60 mg: Black Iron oxide, titanium dioxide
- 80 mg: FD&C Red No. 40, FD&C Yellow No. 6, D&C Yellow No. 10, titanium dioxide

Stability and Storage Conditions

Store in a cool, dry place between 15 and 30°C. Protect from moisture.

AVAILABILITY

Biphentin® (methylphenidate hydrochloride controlled release capsules) is available in capsules that have a white body for all strengths and caps of the following colours for each strength: 10 mg (light turquoise blue), 15 mg (orange), 20 mg (yellow), 30 mg (blue violet), 40 mg (pink), 50 mg (light green), 60 mg (iron grey) and 80 mg (reddish orange). Each capsule is imprinted with **Biphentin** and a number corresponding to the strength, in mg.

Biphentin is supplied in opaque plastic bottles of 100 capsules for 10, 15, 20, 30, and 40 mg strengths and in opaque plastic bottles of 50 capsules for 50, 60 and 80 mg strengths.

PHARMACOLOGY

The pharmacological properties of methylphenidate are similar to those of the amphetamines. However in contrast to amphetamines, methylphenidate is a mild CNS stimulant with more prominent effects on mental than motor activities.

Methylphenidate increases extracellular concentrations of dopamine and norepinephrine by inhibiting their neuronal reuptake, and is also an inhibitor of monoamine oxidase.

The behavioural and cognitive symptoms in ADHD and their response to stimulants are considered to reflect activity of dopaminergic and noradrenergic systems. Dopamine transporter binding sites are increased in the brains of ADHD patients and there is evidence for a genetic basis for this finding. Methylphenidate has been shown to both increase extracellular dopamine in the human brain and to reduce the number of dopamine transporter binding sites in patients with ADHD.

Methylphenidate exists as erythro and threo isomers but only the threo isomer possesses motor stimulant effects. Since both isomers inhibit monoamine oxidase, this suggests that this activity is not a primary mechanism of action of the *dl*-threo isomer when used clinically in ADHD.

dl-threo methylphenidate displays enantioselective pharmacokinetics. After administration of *dl*-methylphenidate, plasma concentrations of *d*-methylphenidate are greater than those of *l*-methylphenidate, due to preferential pre-systemic metabolism of the *l*-enantiomer to *l*-ritalinic acid. In addition, presence of the *d*-enantiomer inhibits the conversion of the *l*-enantiomer to ritalinic acid.

Clinical Trials

Biphentin[®] (methylphenidate hydrochloride controlled release capsules) was demonstrated to be effective in the treatment of ADHD in three double-blind, active- and placebo-controlled studies involving children (≥ 6 years of age) and adults who met the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Illness, 4th edition (DSM-IV) criteria for ADHD.

Table 4: Study Demographics, Trial Design and Results of Study 1 (022-004) – Children ≥ 6 Years of Age with ADHD

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
Study 1 (022-004)	Randomized, double-blind crossover vs. IR methylphenidate	10 - 60 mg/day [†] , oral, 5 to 11 weeks	n = 90	11.0 (6.4 to 17.5) years	M = 74 F = 16
Primary Endpoints		Associated value and statistical significance for Biphentin vs. Baseline		Associated value and statistical significance for IR Methylphenidate vs. Baseline	
Investigator Clinical Global Impressions (<i>Global Improvement from very much improved [1] to very much worse [7]</i>)		Biphentin 2.3 \pm 1.1 73.1 % rated as “much improved” or “very much improved” (Biphentin vs. IR Methylphenidate, p = 0.1684)		IR Methylphenidate 2.3 \pm 1.3 81.0 % rated as “much improved” or “very much improved”	
Conners' Parent Rating Scale (<i>ADHD Index T score</i>) (performed at approximately 12 hours post-morning dose)		Baseline 70.4 \pm 10.2 Biphentin 56.6 \pm 10.9 (p = 0.0001) (Biphentin vs. IR Methylphenidate, p = 0.6635)		Baseline 70.4 \pm 10.2 IR Methylphenidate 56.8 \pm 11.0 (p = 0.0001)	
Conners' Teacher Rating Scale (<i>ADHD Index T score</i>) (composite score of morning and afternoon behaviour)		Baseline 67.2 \pm 10.6 Biphentin 56.3 \pm 10.2 (p = 0.0001) (Biphentin vs. IR Methylphenidate, p = 0.0002)		Baseline 67.2 \pm 10.6 IR Methylphenidate 52.8 \pm 8.5 (p = 0.0001)	

[†]The doses of Biphentin and IR Methylphenidate were titrated in each phase of the study and the final mean doses were very similar (32.0 \pm 8.4 mg and 32.5 \pm 8.6 mg/day respectively).

Table 5: Study Demographics, Trial Design and Results of Study 2 (022-005) - Children ≥ 6 Years of Age with ADHD

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
Study 2 (022-005)	Randomized, double-blind crossover vs. IR methylphenidate vs. placebo	20 – 60 mg/day [†] , oral, 3 weeks	n = 17*	11.3 (6.8 to 15.3) years	M = 15 F = 2
Primary Endpoints		Associated value and statistical significance (±SD) for Biphentin vs. Placebo		Associated value and statistical significance (±SD) for IR Methylphenidate vs. Placebo	
Investigator Clinical Global Impressions (Global Improvement from very much improved [1] to very much worse [7])		Placebo 3.88 ± 1.5 Biphentin 2.0 ± 0.8 (p = 0.0001)		Placebo 3.88 ± 1.5 IR Methylphenidate 2.31 ± 1.3 (p = 0.0006)	
		(Biphentin vs. IR Methylphenidate, p = 0.4324)			
Stop Signal Paradigm (Stop Signal Reaction Time [msec])		Placebo 372.2 ± 167.8 Biphentin 247.1 ± 106.4 (p = 0.0001)		Placebo 372.2 ± 167.8 IR Methylphenidate 261.6 ± 146.1 (p = 0.0005)	
		(Biphentin vs. IR Methylphenidate, p = 0.3245)			
IOWA Conners' Rating Scale (Inattention/Overactivity score) (average score over 10 hours post-morning dose)		Placebo 5.4 ± 3.6 Biphentin 2.4 ± 2.9 (p = 0.0001)		Placebo 5.4 ± 3.6 IR Methylphenidate 1.3 ± 0.9 (p = 0.0001)	
		(Biphentin vs. IR Methylphenidate, p = 0.2806)			
Continuous Performance Test (Errors of Omission)		Placebo 60.0 ± 41.5 Biphentin 47.4 ± 50.9 (p = 0.0039)		Placebo 60.0 ± 41.5 IR Methylphenidate 31.0 ± 22.6 (p = 0.0001)	
		(Biphentin vs. IR Methylphenidate, p = 0.2796)			
Arithmetic Test (Number Completed; Number Correct; Percent Correct)		Placebo 22.88; 17.59; 75.81 Biphentin 25.15; 20.53; 81.21 (p = 0.0663; p = 0.0222; p = 0.0352)		Placebo 22.88; 17.59; 75.81 IR Methylphenidate 25.97; 20.65; 77.48 (p = 0.0163; p = 0.0151; p = 0.3585)	
		(Biphentin vs. IR Methylphenidate, p = 0.5124; p = 0.8603; p = 0.2032)			

*18 enrolled, 17 evaluable

[†] Patients were crossed-over between Biphentin and IR Methylphenidate at the same total daily dose (mean 31.2 ± 11.7 mg) which was based on their pre-study methylphenidate dose (or on body weight, if not receiving methylphenidate).

Table 6: Study Demographics, Trial Design and Results of Study 3 (022-008) – Adults with ADHD

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
022-008	Randomized, double-blind crossover vs. placebo	10 - 80 mg/ day, oral, 5 to 11 weeks	n = 50	37.2 (18.8 to 57.1) years	M = 32 F = 18
Primary Endpoints		Associated value (± standard deviation) for Biphentin vs. Baseline		Associated value (± standard deviation) for Placebo vs. Baseline	
Investigator Clinical Global Impressions <i>(Global Improvement from very much improved [1] to very much worse [7])</i>		Biphentin 2.6 ± 1.0 48.7 % rated as “much improved” or “very much improved”		Placebo 3.7 ± 1.4 23.0 % rated as “much improved” or “very much improved”	
		(Biphentin vs. Placebo, p = 0.0015)			
Conners' Adult ADHD Rating Scale - Self <i>(ADHD Index T score)</i>		Baseline 72.3 ± 8.2 Biphentin 60.1 ± 12.7		Baseline 72.3 ± 8.2 Placebo 66.9 ± 12.5	
		(Biphentin vs. Placebo, p = 0.0083)			
Conners' Adult ADHD Rating Scale - Observer <i>(ADHD Index T score)</i>		Baseline 73.4 ± 6.8 Biphentin 62.5 ± 13.4		Baseline 73.4 ± 6.8 Placebo 66.6 ± 14.1	
		(Biphentin vs. Placebo, p = 0.1404)			

TOXICOLOGY

Toxicology and carcinogenesis studies with methylphenidate hydrochloride were performed in rats and mice. Methylphenidate was administered for 2 years at doses of 0, 100, 500 or 1,000 ppm in the feed of rats and 0, 50, 250 and 500 ppm to mice. The average amount of methylphenidate consumed per day was estimated to be 4-47 mg/kg/day for rats and 5-67 mg/kg/day for mice. An increase of benign tumours of the liver, and increased liver weights, were observed in mice at the high dose. Increased incidences of neoplasms were not seen in the rats. Methylphenidate was not mutagenic in the Salmonella assay system. Epidemiology studies of methylphenidate have found no evidence of a carcinogenic effect in humans.

A reproductive toxicity study in mice demonstrated that doses of 18, 75 and 160 mg/kg/day did not produce any changes in reproductive end points, despite changes in liver weights and male body weights.

In animal studies, no teratogenic effects were seen in rats when given at a dose of 75 mg/kg/day, which are 62.5 and 13.5 times the maximum recommended human dose on a mg/kg and mg/m² basis respectively. In another study, however, methylphenidate was shown to be teratogenic in rabbits when given at a dose of 200 mg/kg/day which are approximately 167 times and 78 times higher than the maximum recommended human dose on a mg/kg and mg/m² basis respectively.

BIBLIOGRAPHY

1. Albertson TE. Section II: Specific poisons and drugs: diagnosis and treatment. Amphetamines. In: Olson KR, editor. *Poisoning and Drug Overdose*. 4th ed. New York: McGraw-Hill; 2004. p. 72-4.
2. Barkley RA, DuPaul GJ, McMurray MB. Attention deficit disorder with and without hyperactivity: Clinical response to three dose levels of methylphenidate. *Pediatrics* 1991;87(4):519-31.
3. Barkley RA, Cook Jr. EH, Diamond A, Zametkin A, Thapar A, Teeter A, et al. International consensus statement on ADHD. January 2002. *Clin Child Fam Psychol Rev* 2002 Jun;5(2): 89-111.
4. Brown RT, Borden KA, Clingerman SR. Adherence to methylphenidate therapy in a pediatric population. *Psychopharmacol Bull* 1985;21(1):28-36.
5. Canadian Paediatric Society, Mental Health Committee: Use of methylphenidate for attention deficit hyperactivity disorder. *CMAJ* 1990;142(8):817-8.
6. Dalby JT, Kinsbourne M, Swanson JM. Self-paced learning in children with attention deficit disorder with hyperactivity. *J Abnorm Child Psychol* 1989;17:269-75.
7. Davy T, Rodgers CL. Stimulant medication and short attention span: a clinical approach. *J Dev Behav Pediatr* 1989;10:313-8.
8. Dougherty DD, Bonab AA, Spencer TJ, Rauch SL, Madras BK, Fischman AJ. Dopamine transporter density in patients with attention deficit hyperactivity disorder. *The Lancet* 1999;354:2132-3.
9. Douglas VI, Barr RG, Amin K, O'Neill ME, Britton BG. Dosage effects and individual responsiveness to methylphenidate in attention deficit disorder. *J Child Psychol Psychiatry* 1988;29(4):453-75.
10. Douglas VI, Barr RG, O'Neill ME, Britton BG. Short-term effects of methylphenidate on the cognitive, learning and academic performance of children with attention deficit disorder in the laboratory and the classroom. *J Child Psychol Psychiatry* 1986;27(2):191-211.
11. Dresel S, Krause J, Krause KH, LaFougere C, Brinkbäumer K, Kung HF, et al. Attention deficit hyperactivity disorder: binding of [^{99m}Tc] TRODAT-1 to the dopamine transporter before and after methylphenidate treatment. *Eur J Nucl Med* 2000; 27(10):1518-24.
12. Fitzpatrick PA, Klorman R, Brumaghim JT, Borgstedt AD. Effects of sustained-release and standard preparations of methylphenidate on attention deficit disorder. *J Amer Acad Child Adolesc Psychiat (USA)* 1992;31(2):226-34.

13. Gualtieri CT, Hicks RE, Kennerly P, Schroeder SR, Breese GR. Clinical correlates of methylphenidate blood levels. *Ther Drug Monit* 1984;6:379-92.
14. Hoffman BB. Catecholamines, sympathomimetic drugs, & adrenergic receptor antagonists. Miscellaneous adrenergic agonists. In: Hardman JG, Limbird LE, Goodman Gilman A, editors. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York: McGraw-Hill; 2001. p. 235-8.
15. Hungund BL, Perel JM, Hurwic MJ, Sverd J, Winsberg BG. Pharmacokinetics of methylphenidate in hyperkinetic children. *Br J Clin Pharmacol* 1979;8:571-6.
16. Jain U, Hechtman L, Quinn D, Sacks D, Mutch D, Turgay A, Wiess M, Yaremko J. Guidelines for the diagnosis and management of ADHD. In: Ross M-E, editor. 1st ed. Toronto, ON: McCleary-McCann Publishers; 2005.
17. Jain U, Hechtman L, Weiss M, Ahmed TS, Reiz JL, Donnelly GAE, et al. Efficacy of a novel biphasic controlled-release methylphenidate formula in adults with attention-deficit/hyperactivity disorder: results of a double-blind, placebo-controlled crossover study. *J Clin Psychiatry* 2007;68(2):268-77.
18. Johnston C, Fine S. Methods of evaluating methylphenidate in children with attention deficit hyperactivity disorder: acceptability, satisfaction, and compliance. *J Pediatric Psychol* 1993;18:717-30.
19. Kauffman RE, Smith-Wright D, Reese, CA, Simpson R, Jones F. Medication compliance in hyperactive children. *Pediatric Pharmacol* 1981;1:231-7.
20. Kessler S. Drug therapy in attention-deficit hyperactivity disorder. *South Med J* 1996;89(1):33-8.
21. Kloner RA, Rezkalla SH. Substance abuse and the heart. In: Topol EJ, Califf RM, Isner J, Prystowsky EN, Swain J, Thomas J, Thompson P, Young JB, Nissen S, editors. *Textbook of cardiovascular medicine. The core information essential for day-to-day clinical practice*. 2nd ed. New York: Lippincott Williams and Williams; 2002. p. 874.
22. Krause K-H, Dresel SH, Krause J, Kung HF, Tatsch K. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. *Neuroscience Letters* 2000;285:107-10.
23. Malone MA, Swanson JM. Effects of methylphenidate on impulsive responding in children with attention-deficit hyperactivity disorder. *J Child Neurol* 1993;8:157-63.

24. Malone MA, Kershner JR, Siegel L. The effects of methylphenidate on levels of processing and laterality in children with attention deficit disorder. *J Abnorm Child Psychol* 1988;16: 379-95.
25. Quinn D, Bode T, Reiz JL, Donnelly GAE and Darke AC. Single-dose pharmacokinetics of multilayer-release methylphenidate and immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. *J Clin Pharmacol* 2007;47:760-6.
26. Schachar RJ, Tannock R, Cunningham C, Corkum PV. Behavioral, situational, and temporal effects of treatment of ADHD with methylphenidate. *J Am Acad Child Adolesc Psychiatry* 1997;36:754-63.
27. Schachar R, Ickowicz A, Crosbie J, Donnelly GAE, Reiz JL, Miceli PC, et al. Cognitive and behavioral effects of multilayer-release methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2008; 18(1):11-24.
28. Searight HR, Burke JM, Rottnek F. Adult ADHD: evaluation and treatment in family medicine. *Am Fam Physician* 2000;62(9):2077-86, 2091-2.
29. Shaywitz S, Shaywitz B. Diagnosis and management of attention deficit disorder: A pediatric perspective. *Pediatr Clin North Am* 1984;31(2):429-57.
30. Solanto MV. Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. *Behav Brain Res* 1998;94(1):127-52.
31. Solanto MV. Dopamine dysfunction in ADHD: Integrating clinical and basic neuroscience research. *Behav Brain Res* 2002;130:65-71.
32. Sunohara GA, Voros JG, Malone MA, Taylor MJ. Effects of methylphenidate in children with attention deficit hyperactivity disorder: A comparison of event-related potentials between medication responders and non-responders. *Int J Psychophysiol* 1997;27:9-14.
33. Tannock R, Schachar R, Carr RP, Logan G. Dose-response effects of methylphenidate on academic performance and overt behaviour in hyperactive children. *Pediatrics* 1989;84: 648-57.
34. Tannock R, Schachar R, Carr RP, Chajczyk D, Logan DG. Effects of methylphenidate on inhibitory control in hyperactive children. *J Abnorm Child Psychol* 1989;17:473-91.
35. Tannock R, Schachar R. Methylphenidate and cognitive perseveration in hyperactive children. *J Child Psychol Psychiat* 1992;33:1217-28.

36. Tannock R, Schachar R, Logan G. Methylphenidate and cognitive flexibility: dissociated dose effects in hyperactive children. *J Abnorm Child Psychol* 1995;23:235-66.
37. Taylor MJ, Voros JG, Logan, WJ, Malone MA. Changes in event-related potentials with stimulant medication in children with attention deficit hyperactivity disorder. *Bioavailability Psychol* 1993;36:139-56.
38. The Tourettes's Syndrome Study Group. Treatment of ADHD in children with tics. A randomized controlled trial. *Neurology* 2002;58(4):527-36.
39. Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, Ding YS, et al. Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. *Am J Psychiatry* 1998;155(10):1325-31.
40. Volkow ND, Wang G-J, Fowler JS, Logan J, Gerasimov M, Maynard L, et al. Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. *J Neurosci* 2001;21:RC121 (1-5).
41. Volkow ND, Wang GJ, Fowler JS, Logan J, Francheschi D, Maynard L, et al. Relationship between blockade of dopamine transporters by oral methylphenidate and the increases in extracellular dopamine: therapeutic implications. *Synapse* 2002;43(3):181-7.
42. Weiss M, Murray C. Assessment and management of attention-deficit hyperactivity disorder in adults. *CMAJ* 2003;168(6):715-22.
43. Weiss M, Hechtman L, Turgay A, Jain U, Quinn D, Ahmed T, et al. Once-daily multilayer-release methylphenidate in a double-blind, crossover comparison to immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2007;17(5):675-88.
44. Wender PH, Reimherr FW, Wood D, Ward M. A controlled study of methylphenidate in the treatment of attention deficit disorder, residual type, in adults. *Am J Psychiatry* 1985;142: 547-52.
45. Wilens TE, Spencer TJ, Biederman J. A review of the pharmacotherapy of adults with Attention-Deficit/Hyperactivity Disorder. *J Atten Disord* 2002;5(4):189-202.
46. Winsberg BG, Kupietz SS, Sverd J, Hungund BL, Young NI. Methylphenidate oral dose plasma concentrations and behavioural response in children. *Psychopharmacol* 1982;76:329-32.

CONSUMER INFORMATION



Methylphenidate Hydrochloride Controlled Release Capsules

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

Read this information carefully before you / your child start taking Biphentin capsules. Remember, this information does not take the place of your doctor's instructions.

Biphentin, as with other stimulants, can be abused or lead to dependence. Store Biphentin in a secure place and do not give it to anyone other than the person for whom it was prescribed. Selling or giving away Biphentin may harm others and is against the law.

The following have been reported with use of methylphenidate 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 / 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 / your child carefully for heart problems before starting Biphentin.

Your doctor may wish to check you / your child's blood pressure and heart rate regularly during treatment with Biphentin.

Call your doctor right away if you / your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking Biphentin.

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 / your child have, or about a family history of suicide, bipolar illness, or depression.

Call your doctor right away if you / your child have any new or worsening mental symptoms or problems while taking Biphentin,

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:

Biphentin is a once-daily treatment for Attention-Deficit Hyperactivity Disorder (ADHD) in children over 6 years of age and adults. The following information will tell you about ADHD and the use of Biphentin in this condition.

Biphentin contains methylphenidate hydrochloride, which belongs to a group of medicines called central nervous system stimulants. Methylphenidate 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.

What it does:

Biphentin helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD. It is designed to be taken as a single dose at breakfast-time and to help symptoms of ADHD by delivering the active ingredient methylphenidate hydrochloride to the bloodstream, both in the early morning, and later in the day. In the case of children, this allows the daily dose of Biphentin to be taken under parental supervision, without the need for a dose to be taken at school.

Treatment with methylphenidate during childhood and/or adolescence does not appear to result in increased predisposition for addiction. However, central nervous stimulants, including Biphentin, should only be given under close medical supervision to individuals whose condition has been properly diagnosed, since abuse of methylphenidate hydrochloride can lead to dependence.

When it should not be used:

Biphentin should NOT be taken if you / your child:

- are allergic to methylphenidate hydrochloride or any of the other ingredients in Biphentin (See "**What the important nonmedicinal ingredients are**");
- have anxiety, tension or agitation;
- have glaucoma (increased eye pressure);
- have, or there is a family history of, motor 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 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).

What the medicinal ingredient is:

Methylphenidate Hydrochloride

What the important nonmedicinal ingredients are:

Colouring, gelatin, hydroxypropyl methylcellulose, methyl acrylic acid copolymer, polyethylene glycol, sugar beads, talc, iron oxide, titanium dioxide and triethyl citrate.

What dosage forms it comes in:

Biphentin controlled release capsules are available in eight strengths: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 80 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Drug Dependence**
Abuse of methylphenidate hydrochloride 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. Since some serious heart problems alone can carry an increased risk of sudden death, **Biphentin** generally should not be used in children, adolescents or adults with known serious structural heart abnormalities.

BEFORE you use **Biphentin** talk to your doctor or pharmacist if you / your child:

- have mild high blood pressure, heart problems or heart defects;
- thyroid disorders;
- have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms);
- are being treated for depression or have symptoms of depression, such as feelings of sadness, worthlessness and hopelessness;
- have been diagnosed with psychosis (have abnormal thoughts or visions, hear abnormal sounds);
- have been diagnosed with bipolar disorder;
- do strenuous exercise; or
- take other drugs for ADHD.

Tell your doctor if you have a family history of suicide or any of the conditions or symptoms listed above.

Your doctor may wish to check you / your child carefully for heart problems before starting **Biphentin**.

Before taking **Biphentin** tell your doctor if you are pregnant or plan to become pregnant. **Biphentin** should not be used during pregnancy. Mothers taking **Biphentin** should not breast-feed their babies.

Contact your doctor immediately if you / your child develop any of the above conditions or symptoms while taking **Biphentin**.

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 **Biphentin** 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 **Biphentin** with monoamine oxidase (MAO) inhibitors.

You should avoid alcoholic drinks while taking **Biphentin**. You / your child should avoid taking prescription or over the counter medicines containing alcohol, such as some cough syrups.

Biphentin may change the way you / 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 **Biphentin**.

PROPER USE OF THIS MEDICATION

Biphentin capsules must be swallowed whole with water or other liquids and should never be crushed or chewed.

Biphentin capsules are to be taken once per day, at breakfast-time. Your doctor determines the appropriate dose of **Biphentin** according to your or your child’s individual needs. In order to receive the most benefits from **Biphentin**, it is important that it be taken only as directed by your doctor – only the amount of medication and at the time intervals and for the time period that your doctor has prescribed.

It may be necessary for you to take more than one capsule at the same time, in order to receive the total daily dosage prescribed by your doctor.

If necessary, the capsule contents may be sprinkled on these soft foods: apple sauce, ice cream or yogurt, but the beads must not be chewed or crushed.

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

Treatment with **Biphentin**, or other stimulants, should be combined with other measures, such as psychological counselling, educational and social measures, as part of a total treatment program.

Usual dose for children and adolescents (6 -18 years of age) and adults (> 18 years of age):

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

Your doctor may wish to check you / your child's blood pressure and heart rate regularly during treatment with **Biphentin**.

Overdose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects with **Biphentin** were headache, sleeplessness, nervousness, anxiety, loss of appetite, stomach discomfort and nausea (feeling sick). Other side effects not listed above may occur in some patients.

Contact your doctor if any of the following unwanted effects are experienced: breathing difficulties, bruising, chest pain, confusion, convulsions, fast heartbeat, abnormal thinking or hallucinations, muscle twitching or tics, sore throat and fever, sudden high fever, sweating, vomiting.

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

Tell your doctor if you / your child have blurred vision when taking **Biphentin**.

Biphentin may affect your ability to drive or operate machinery.

This is not a complete list of side effects. For any unexpected effects while taking **Biphentin**, contact your doctor or pharmacist.

HOW TO STORE IT

Store **Biphentin** in a secure place and do not give it to anyone other than the person for whom it was prescribed.

Store at room temperature (15-30°C). Protect from moisture. Protect from high humidity. **Keep out of the reach of children.**

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax: 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
<http://www.purdue.ca/products>
or by contacting the manufacturer, Purdue Pharma, at:
1-800-387-5349

This leaflet was prepared by Purdue Pharma.

Last revised: June 19, 2009