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

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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

ACTION AND CLINICAL PHARMACOLOGY

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

Absorption

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

Distribution

The extent of methylphenidate distribution in humans is unknown.

Elimination

Methylphenidate is excreted almost entirely in the urine.

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).

Methylphenidate excretion into breast milk has been noted in two case reports, where the calculated relative infant dose was ≤ 0.2% of the weight adjusted maternal dose.

Metabolism

The primary route of metabolism for methylphenidate is desterification 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-piperidineacetic 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%).

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

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. 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 **PHARMACEUTICAL INFORMATION**, Non-medicinal Ingredients (all strengths).

- 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**).

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.

Cardiovascular

Misuse and Serious Cardiovascular Adverse Events

The misuse of central nervous system stimulants may cause serious cardiovascular adverse events and sudden death.

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.

Assessing Cardiovascular Status in Patients being Treated with Sympathomimetic Medications
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.

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 and Other Cardiovascular Conditions

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

Biphentin should not be used to treat severe exogenous or endogenous depression.

Fatigue

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

Pre-Existing Psychosis

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

Screening Patients for Bipolar Disorder

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 post-marketing 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.

Suicidal Behaviour and Ideation

There have been post-marketing reports of suicide-related events in patients treated with ADHD drugs, including cases of ideation, attempts, and very rarely, completed suicide. The mechanism of this risk is not known. ADHD and its related co-morbidities may be associated with increased risk of suicidal ideation and/or behaviour. Therefore, it is recommended that patients treated with ADHD drugs be monitored for signs of suicide-related behaviour, including at dose initiation/optimization and drug discontinuation. Patients should be encouraged to report any distressing thoughts or feelings at any time to their healthcare professional.

Patients with emergent suicidal ideation and behaviour should be evaluated immediately. The physician should initiate appropriate treatment of the underlying psychiatric condition and consider a possible change in the ADHD treatment regimen (see **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**).

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.

Sexual Function/Reproduction

Priapism

Prolonged and painful erections requiring immediate medical attention (sometimes including surgical intervention), have been reported with methylphenidate products, in both pediatric and adult patients (see **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**). Priapism can develop after some time on methylphenidate, often subsequent to an increase in dose. Priapism has also appeared during a period of methylphenidate withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained erections or frequent and painful erections should seek immediate medical attention.

Vascular

Peripheral Vasculopathy, including Raynaud's Phenomenon

Stimulants used to treat ADHD, such as **Biphentin**, are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

Special Populations

Pregnant Women

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.

Nursing Women

Case reports showed that methylphenidate was distributed into breast milk reaching a milk-to-plasma ratio of approximately 2.5 (see **ACTION AND CLINICAL PHARMACOLOGY, Elimination**). A risk to the suckling child cannot be excluded. A decision should be made whether to abstain from breast-feeding or to abstain from **Biphentin** therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman.

There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate.

Children (< 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 **INDICATIONS, Long-term Use**).

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.

Caution should be exercised in prescribing concomitant drugs.

Monitoring and Laboratory Tests

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

Because methylphenidate may affect performance, patients should be cautious when driving or operating machinery. Patients should be cautioned accordingly until they are reasonably certain that **Biphentin** does not adversely affect their ability to engage in such activities.

DRUG INTERACTIONS

Overview

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.

Anti-hypertensive Drugs

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

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 including sudden death have been reported in concomitant use with clonidine. In these cases, no causality for the combination could be established because of insufficient data.

ADVERSE 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.

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. Table 1 and Table 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.

Table 1: Adverse Events[a] with ≥1% Incidence in Clinical Trials in Children 6-11 Years of Age

	Biphentin % (n = 68)	IR Methylphenidate % (n = 68)
General Disorders and Administration Site Conditions		
headache	11.8	8.8
abdominal pain	8.8	8.8
pain	2.9	1.5
asthenia	1.5	2.9
malaise	1.5	0.0
chills	1.5	4.4
pyrexia	1.5	1.5
hypersensitivity	1.5	0.0
rebound effect	4.4	1.5
neoplasm (benign nasal polyp)	0.0	1.5
Eye Disorders		
visual impairment	1.5	0.0

Table 1: Adverse Events[a] with ≥1% Incidence in Clinical Trials in Children 6-11 Years of Age

	Biphentin % (n = 68)	IR Methylphenidate % (n = 68)
Infections and Infestations		
influenza	5.9	7.4
infection	2.9	2.9
Nervous System Disorders		
somnolence	11.8	4.4
tic (verbal)	2.9	0.0
speech disorder	2.9	1.5
tic (motor)	2.9	1.5
dizziness	1.5	0.0
depersonalization	0.0	1.5
hallucinations	0.0	1.5
hyperkinesia	0.0	1.5
tremor	0.0	1.5
Gastrointestinal Disorders		
anorexia	22.1	19.1
nausea	5.9	2.9
vomiting	2.9	1.5
diarrhea	0.0	2.9
Metabolism and Nutrition Disorders		
increased appetite	2.9	0.0
Psychiatric Disorders		
insomnia	22.1	14.7
nervousness	8.8	8.8
apathy	7.4	4.4
depression	7.4	4.4
affect lability	2.9	8.8
obsessive-compulsive disorder	2.9	2.9
sleep disorder	1.5	2.9
euphoric mood	1.5	1.5
anxiety	1.5	0.0
stereotypy	1.5	0.0
agitation	0.0	1.5
Respiratory, Thoracic and Mediastinal Disorders		
pharyngitis	2.9	2.9
asthma	1.5	1.5
cough	1.5	5.9
rhinitis	0.0	1.5
bronchitis	0.0	1.5

Table 1: Adverse Events[a] with ≥1% Incidence in Clinical Trials in Children 6-11 Years of Age

	Biphentin % (n = 68)	IR Methylphenidate % (n = 68)
Skin and Subcutaneous Tissue Disorders		
rash	5.9	2.9
eczema	1.5	0.0
photosensitivity reaction	1.5	0.0
skin discolouration	1.5	0.0
Vascular Disorders		
hypertension	1.5	0.0
vasodilatation	1.5	0.0
Special Senses		
conjunctivitis	1.5	0.0
corneal lesion	1.5	0.0
otitis media	1.5	0.0

a. 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 children in the **Biphentin** clinical trials.

Table 2: Adverse Events[a] with ≥1% Incidence in Clinical Trials in Adolescents 12-18 Years of Age

	Biphentin % (n = 40)	IR Methylphenidate % (n = 40)
General Disorders and Administration Site Conditions		
asthenia	2.5	2.5
thirst	0.0	2.5
pain	0.0	2.5
Cardiac Disorders		
palpitations	2.5	0.0
tachycardia	0.0	2.5
Nervous System Disorders		
headache	25.0	22.5
somnolence	15.0	7.5
dizziness	7.5	10.0
tic (vocal)	2.5	2.5
vertigo	2.5	2.5
syncope	0.0	2.5
rebound effect	0.0	2.5

Table 2: Adverse Events[a] with ≥1% Incidence in Clinical Trials in Adolescents 12-18 Years of Age

	Biphentin % (n = 40)	IR Methylphenidate % (n = 40)
Gastrointestinal Disorders		
anorexia	7.5	27.5
abdominal pain	5.0	10.0
nausea	5.0	5.0
increased appetite	5.0	12.5
vomiting	2.5	2.5
diarrhea	2.5	0.0
Infection and Infestations		
influenza	7.5	7.5
infection	0.0	2.5
Musculoskeletal and Connective Tissue Disorders		
arthralgia	2.5	2.5
Respiratory, Thoracic and Mediastinal Disorders		
pharyngitis	5.0	2.5
cough increased	0.0	5.0
asthma	0.0	2.5
sinusitis	0.0	2.5
Psychiatric Disorders		
nervousness	27.5	25.0
insomnia	7.5	12.5
depersonalization	7.5	0.0
depression	2.5	5.0
affect lability	5.0	5.0
sleep disorder	2.5	2.5
apathy	2.5	0.0
obsessive-compulsive disorder	2.5	0.0
anxiety	0.0	2.5
neurosis	0.0	2.5
Skin and Subcutaneous Tissue Disorders		
pruritus	0.0	2.5
Reproductive System and Breast Disorders		
dysmenorrhea	0.0	2.5

a. 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 adolescents in the **Biphentin** clinical trials.

Table 3: Adverse Events[a] with ≥1% Incidence in Clinical Trials in Adults

	Biphentin % (n = 50)	Placebo % (n = 50)
General Disorders and Administration Site Conditions		
Body as a Whole		
asthenia	8.0	10.0
pyrexia	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 Disorders		
tachycardia	6.0	4.0
palpitations	2.0	2.0
Ear and Labyrinth Disorders		
ear disorder	2.0	0.0
Eye Disorders		
visual impairment	2.0	0.0
Nervous System Disorders		
headache	28.0	24.0
akathisia	6.0	0.0
dizziness	4.0	2.0
hypertension	4.0	2.0
somnolence	2.0	4.0
twitching	2.0	2.0
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
Gastrointestinal Disorders		
anorexia	26.0	6.0
nausea	20.0	8.0
dry mouth	12.0	2.0
abdominal pain	4.0	6.0
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

Table 3: Adverse Events[a] with ≥1% Incidence in Clinical Trials in Adults

	Biphentin % (n = 50)	Placebo % (n = 50)
Metabolic and Nutrition Disorders		
weight decreased	2.0	0.0
Musculoskeletal and Connective Tissue Disorders		
arthralgia	2.0	2.0
myalgia	0.0	2.0
Psychiatric Disorders		
nervousness	24.0	4.0
insomnia	22.0	10.0
anxiety	18.0	0.0
affect lability	10.0	2.0
depression	8.0	2.0
agitation	6.0	4.0
abnormal thinking	4.0	0.0
depersonalization	2.0	2.0
confusional state	2.0	0.0
neurosis	2.0	0.0
Respiratory, Thoracic and Mediastinal Disorders		
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 Subcutaneous Tissue Disorders		
hyperhidrosis	6.0	0.0
ecchymosis	0.0	2.0
Vascular Disorders		
peripheral vascular disease	2.0	0.0

a. 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.

Post-Marketing Adverse Drug Reactions

Suicidal Behaviour and Ideation

There have been post-marketing reports of suicide-related events, including completed suicide, suicide attempt, and suicidal ideation in patients treated with ADHD drugs. In some of these reports, comorbid conditions may have contributed to the event (see **WARNINGS**, **Suicidal Behaviour and Ideation).**

Two one-week, placebo-controlled clinical studies have been conducted post-market with **Biphentin (10 to 40 mg)** in pediatric patients; one in children aged 6 to 12 years, and one in children and adolescents aged 6 to 17 years. The two studies evaluated a total of 256 patients with ADHD. From these studies, the following events have also been reported with **Biphentin:**

Investigations: blood creatine phosphokinase increased, electrocardiogram QT prolonged

Metabolism and Nutrition Disorders: decreased appetite

Musculoskeletal and Connective Tissue Disorders: musculoskeletal stiffness

Nervous System Disorders: lethargy

Psychiatric Disorders: crying, irritability, oppositional defiant disorder, psychomotor hyperactivity, tearfulness

Adverse Events Reported with Other Methylphenidate Hydrochloride Products

Nervousness and insomnia are the most common adverse reactions reported with 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); acute hepatic failure; abdominal pain; anemia; angina; anorexia; blood pressure and pulse changes, both up and down; bradycardia; drowsiness; headache; leukopenia; nausea; pancreatitis; Stevens-Johnson Syndrome; sudden cardiac death; tachycardia; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has also been reported.

The following events have also been reported with methylphenidate products, including **Biphentin**: alopecia, angioedema, blurred vision, convulsions, dizziness, dyskinesia, erythema, flushing, hallucinations, hypersensitivity, mydriasis, psychotic disorder, tremor and Raynaud's phenomenon.

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., ranging from transaminase elevation to hepatic coma); isolated cases of cerebral arteritis and/or occlusion. 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

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

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, diarrhea, euphoria, flushing, hallucinations, headache, hyperpyrexia, hyperreflexia, hypertension, muscle twitching, mydriasis and dryness of mucus membranes, nausea, palpitations, rhabdomyolysis, hyperhidrosis, tachycardia, tachypnea, tremors and vomiting.

Treatment consists of providing supportive measures. The patient must be protected against self-injury and against external stimuli that would exacerbate overstimulation already present. Do not induce vomiting pre-hospital because of the risk of abrupt onset of seizures. 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 overdosage has not been established.

The controlled release of methylphenidate from **Biphentin®** capsules 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.

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 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. The capsule contents (beads) should also not be crushed or chewed.

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

Not recommended in children under 6 years since safety and efficacy in this age group have not been established.

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 10 mg/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.

Geriatrics

No data are available in elderly (>65 years of age).

Hepatic Insufficiency

There is no experience with the use of methylphenidate 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 metabolite, inactive ritalinic acid, is predominantly (80%) cleared through the urine.

Missed Dose

If a dose of **Biphentin** is missed, the patient should be instructed to take the next dose in the usual amount at the usual time the next morning. Patients should be instructed not to take an afternoon dose and not to double dose.

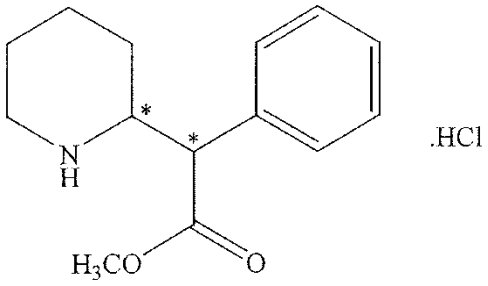
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: methylphenidate hydrochloride

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

Structural Formula:



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

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°C – 226°C

Non-medicinal Ingredients (all strengths): ammonio methacrylate copolymer, type B; gelatin[a], hydroxypropyl methylcellulose, methacrylic acid and ethyl acrylate copolymer, polyethylene glycol, sugar spheres, talc, titanium dioxide and triethyl citrate

a. Colourant Ingredients in the Capsule Shells:

10 mg: FD&C Blue No. 1

15 mg: D&C Red No.28, D&C Yellow No. 10, FD&C Red No. 40

20 mg: D&C Red No. 33, D&C Yellow No. 10

30 mg: FD&C Blue No. 1, FD&C Red No. 3

40 mg: D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40

50 mg: D&C Yellow No. 10, FD&C Green No. 3

60 mg: Black iron oxide

80 mg: FD&C Red No. 40, FD&C Yellow No. 6, D&C Yellow No. 10

Stability and Storage Conditions

Store in a cool, dry place between 15°C and 30°C. Protect from moisture. **Keep Biphentin out of sight and reach of children and pets.**

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[a], oral, 5 to 11 weeks[b]	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 *(Global Improvement from very much improved [1] to very much worse [7])*	Biphentin 2.3 ± 1.1 73.1 % rated as "much improved" or "very much improved"	IR Methylphenidate 2.3 ± 1.3 81.0 % rated as "much improved" or "very much improved"
	(Biphentin vs. IR Methylphenidate, p = 0.1684)	
Conners' Parent Rating Scale *(ADHD Index T score)* (performed at approximately 12 hours post-morning dose)	Baseline 70.4 ± 10.2 Biphentin 56.6 ± 10.9 (p = 0.0001)	Baseline 70.4 ± 10.2 IR Methylphenidate 56.8 ± 11.0 (p = 0.0001)
	(Biphentin vs. IR Methylphenidate, p = 0.6635)	
Conners' Teacher Rating Scale *(ADHD Index T score)* (composite score of morning and afternoon behaviour)	Baseline 67.2 ± 10.6 Biphentin 56.3 ± 10.2 (p = 0.0001)	Baseline 67.2 ± 10.6 IR Methylphenidate 52.8 ± 8.5 (p = 0.0001)
	(Biphentin vs. IR Methylphenidate, p = 0.0002)	

a. 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 ± 8.4 mg and 32.5 ± 8.6 mg/day respectively).

b. Represents titration to optimal effect (one to three weeks), followed by a one-week stable dose period, and then two weeks of treatment on that dose; crossover to other treatment with titration (one to three weeks) followed by two weeks treatment.

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[a], oral, 3 weeks[b]	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)	

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[a], oral, 3 weeks[b]	n = 17*	11.3 (6.8 to 15.3) years	M = 15 F = 2

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

a. 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).

b. Represents 1-week on each treatment

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[a]	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 *(Global Improvement from very much improved [1] to very much worse [7])*	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 *(ADHD Index T score)*	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 *(ADHD Index T score)*	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)	

a. Represents titration to optimal effect (one to three weeks), followed by a one-week stable dose period, and then two weeks of treatment on that dose; crossover to other treatment with titration (one to three weeks) followed by two weeks treatment.

TOXICOLOGY

Carcinogenicity

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.

Mutagenicity

Methylphenidate was not mutagenic in the Salmonella assay system. Epidemiology studies of methylphenidate have found no evidence of a carcinogenic effect in humans.

Teratogenicity

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/m^2 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/m^2 basis respectively.

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6. 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.

PART III: CONSUMER INFORMATION

Biphentin®
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.

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, adolescents 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 in the morning 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 ever had heart problems – such as a heart attack, irregular heartbeat, chest pain (angina), heart failure, heart disease or were born with a heart problem;
- 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 moderate to severe high blood pressure;
- have arteriosclerosis (hardened arteries);
- have hyperthyroidism (an overactive thyroid gland); or
- are taking or have taken within the past 14 days, monoamine oxidase inhibitors (a type of drug, see **INTERACTIONS WITH THIS MEDICATION**).

What the medicinal ingredient is:
methylphenidate hydrochloride

What the nonmedicinal ingredients are:
ammonio methacrylate copolymer, type B; gelatin, hydroxypropyl methylcellulose, methacrylic acid and ethyl acrylate copolymer, polyethylene glycol, sugar spheres, talc, titanium dioxide and triethyl citrate.

In addition, the capsule shells also contain the following:

10 mg - FD&C Blue No. 1

15 mg - D&C Red No.28, D&C Yellow No.10, FD&C Red No. 40

20 mg - D&C Red No. 33, D&C Yellow No. 10

30 mg - FD&C Blue No. 1, FD&C Red No. 3

40 mg - D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40

50 mg - D&C Yellow No. 10, FD&C Green No. 3

60 mg - black iron oxide

80 mg - FD&C Red No. 40, FD&C Yellow No. 6, D&C Yellow No. 10

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.

The following have been reported with use of Biphentin 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**

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.

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 have any signs of heart problems such as chest pain, shortness of breath, or fainting while taking Biphentin.

2. Mental (Psychiatric) problems:
- **new or worse thoughts or feelings related to suicide (thinking about or feeling like killing yourself) and suicide actions (suicide attempt, suicidal ideation and completed suicide)**
- **new or worse bipolar illness, characterized by extreme mood swings, with periods of mania (unusually excited, over-active or un-inhibited) alternating with periods of depression (feelings of sadness, worthlessness or hopelessness)**
- **new or worse aggressive behavior or hostility**
- **new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms.**

These new or worse mental problems may be more likely to occur if you/your child have mental disorders that you may or may not know about. Tell your doctor about any mental problems or about any personal or family history of suicide, bipolar illness, or depression you or your child have.

A small number of patients taking ADHD drugs may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of suicide, self-harm or harm to others. Those suicidal thoughts or behaviors may occur at any time during treatment, particularly at the start or during dose changes, and also after stopping **Biphentin**. **Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your doctor immediately. Close observation by a doctor is necessary in this situation.**

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.

BEFORE using **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);
- have mental problems or family history of mental problems, including psychosis, mania, bipolar illness, depression, or suicide;
- have circulation problems in fingers and toes, including numbness; feeling cold or pain (this is also known as Raynaud's);
- do strenuous exercise; take other drugs for ADHD;
- have a family history of sudden death or death related to heart problems.

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.

Tell your doctor if you are nursing a baby. If you take **Biphentin**, it can be in your breast milk. You should consult with your doctor to determine whether you should stop breast-feeding or discontinue **Biphentin®**.

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), prevent blood clots (commonly called "blood thinners", e.g., warfarin), or treat hypertension (e.g., ACE inhibitors, beta- or calcium channel blockers). 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, in the morning. 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, drowsiness, 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: confusion, muscle twitching or tics, sudden high fever, vomiting.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor, nurse, or pharmacist		Seek immediate medical help
		Only if severe	In all cases	
Unknown	Sudden signs of heart problems, such as fast heartbeat, palpitations, chest pain, shortness of breath, difficulty breathing, or fainting			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor, nurse, or pharmacist: Only if severe	Talk with your doctor, nurse, or pharmacist: In all cases	Seek immediate medical help
Unknown	Fits (seizures), convulsions			√
	Symptoms of allergic reaction, such as itching, skin rash, swelling of the mouth, face, lips, or tongue or shortness of breath			√
	New Psychotic or Manic Symptoms: - Paranoia, delusions - Hallucinations: seeing, feeling or hearing things that are not real - Mania: feeling unusually excited, over-active, or uninhibited **(see Warnings and Precautions)**		√	
	Raynaud's Phenomenon: - Discoloration of the fingers and toes, pain, sensations of cold and/or numbness		√	
	Aggressive behaviour or hostility		√	
	Suicidal Behaviour: Thoughts or actions about suicide or hurting yourself. **(see Warnings and Precautions)**			√
	Long-lasting (greater than 4 hours in duration) and painful erection of the penis			√

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°C - 30°C). Protect from moisture. **Keep Biphentin out of sight and reach of children and pets.**

Reporting Side Effects

We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at 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 at: http://www.purdue.ca

Or by contacting the manufacturer, Purdue Pharma, at: 1-800-387-4501.

This leaflet was prepared by Purdue Pharma.

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