PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

BIPHENTIN®

Methylphenidate hydrochloride

Controlled-Release Capsules, 10, 15, 20, 30, 40, 50, 60 and 80 mg, Oral

Central Nervous System Stimulant

Elvium Life Sciences

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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	09/2023
4 DOSAGE AND ADMINISTRATION	09/2023
7 WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Serotonin Toxicity	09/2021

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

BIPHENTIN® (methylphenidate hydrochloride controlled-release capsules) is indicated for the 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)

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 health professional who elects to use BIPHENTIN for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see 4.1 Dosing Considerations).

Need for Comprehensive Treatment Program

BIPHENTIN is indicated as an integral part of a total treatment program for ADHD that may include other measures (i.e., psychological, educational, and/or 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 health professional's assessment of the chronicity and severity of the patient's symptoms.

1.1 Pediatrics

Pediatrics (<6 years of age): BIPHENTIN should not be used in children under 6 years of age. No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in children under 6 years of age (see 4.2 Recommended Dose and Dosage Adjustment).
Pediatrics (6 – 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of BIPHENTIN in pediatric patients (6 years of age and older) has been established. Therefore, Health Canada has authorized an indication for pediatric use (see 4.2 Recommended Dose and Dosage Adjustment).

1.2 Geriatrics

Geriatrics (>65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

BIPHENTIN is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- Anxiety, tension
- Agitation
- Thyrotoxicosis
- Advanced arteriosclerosis
- Symptomatic cardiovascular disease
- Moderate to severe hypertension
- Glaucoma
- History of drug abuse

Patients with motor tics or with a family history or diagnosis of Tourette's syndrome (verbal tics) (see 7 WARNINGS AND PRECAUTIONS, Neurologic

- Co-Administration of Monoamine Oxidase Inhibitors (MAOIs): During treatment with monoamine oxidase inhibitors and within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result) (see 9.4 Drug-Drug Interactions, Monoamine Oxidase Inhibitors; 9.1 Serious Drug Interactions).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Drug Dependence – Like other stimulants, BIPHENTIN has the potential to be abused, leading to dependence and tolerance (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- BIPHENTIN 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's response to BIPHENTIN varies widely. 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.
- Patients currently receiving immediate-release formulations of methylphenidate may be converted to the next lower strength, based on the total methylphenidate daily dose. Dosage should, then, be individually and slowly adjusted, to the **lowest effective dosage**.
- The maximum daily dose should not exceed 60 mg for children and adolescents (6 to 18 years) or 80 mg for adults (>18 years).
- Assessing Cardiovascular Status in Patients being Treated with Sympathomimetic Medications

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 2 CONTRAINDICATONS and 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

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. Patients who are considered to need extended treatment with BIPHENTIN should undergo periodic evaluation of their cardiovascular status (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

4.2 Recommended Dose and Dosage Adjustment

- **Pediatrics (<6 years of age):** Health Canada has not authorized an indication for pediatric use in patients less than 6 years of age (see 1.1 Pediatrics).
- **Pediatrics (6 – 18 years of age) and Adults (>18 years of age):** 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 total daily dose may be adjusted in weekly increments of 10 mg/day up to a maximum of 60 mg/day. Patients should establish a routine pattern with regard to meals (see 4.4 Administration).

  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 (>18 years of age):** 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. Patients should establish a routine pattern with regard to meals (see 4.4 Administration).
- **Geriatrics (>65 years of age)**: Health Canada has not authorized an indication for geriatric use (see 1.2 Geriatrics).
- **Patients with Hepatic Insufficiency**: There is no experience with the use of methylphenidate in patients with hepatic insufficiency.
- **Patients with Renal Insufficiency:** There is very limited experience with the use of methylphenidate in patients with renal insufficiency. Renal clearance is not significant for methylphenidate elimination, but the main methylphenidate metabolite, inactive ritalinic acid, is predominantly (80%) cleared through the urine.
- **Long-term use:** There is no evidence available from controlled trials to indicate how long the patient with ADHD should be treated with BIPHENTIN. It is generally agreed that pharmacological treatment of ADHD may be needed for extended periods. The physician who elects to use BIPHENTIN for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy.
- **Dose reduction and discontinuation:** If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or if necessary, discontinue the drug. If little or no improvement is observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

4.4 Administration

BIPHENTIN capsules should be swallowed whole and must never be crushed or chewed.

For patients unable to swallow the capsule, the capsule may be opened, and the entire contents sprinkled onto a tablespoon of applesauce, ice cream or yogurt. Do not sprinkle in liquids. The entire mixture should be consumed immediately or within 30 minutes without chewing and should be discarded if not consumed. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and patients should not take anything less than one capsule per day. Ingestion should be followed by rinsing the mouth with water to ensure that the entire contents are swallowed.

BIPHENTIN may be taken with or without food. However, concomitant food intake has variable effects on methylphenidate exposure. Thus, a regular morning routine should be established, with regard to the content and timing of meals, in order to ensure consistent efficacy and safety (see 9.5 Drug-Food Interactions).

4.5 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 the dose.

5 OVERDOSAGE

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 due to 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 methylphenidate. The amount of methylphenidate production is proportional to the blood alcohol concentration (see 9.2 Drug Interactions Overview

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

Drug-Behavioural Interactions). As with the management of all overdosage, the possibility of multiple drug ingestion, including alcohol, should be considered.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Controlled-release capsules / 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 80 mg	Ammonio methacrylate copolymer, type B; gelatin*, hydroxypropyl methylcellulose, methacrylic acid and ethyl acrylate copolymer, polyethylene glycol, sugar spheres, talc, titanium dioxide and triethyl citrate *Colorant 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

BIPHENTIN 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 the following presentations:

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

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

BIPHENTIN has not been compared to other controlled release methylphenidate preparations on the Canadian market and, therefore, is not interchangeable.

Drug treatment is not indicated in all cases of ADHD and should be considered only in light of the complete history and evaluation. The decision to prescribe BIPHENTIN should depend on the health professional'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.

Fatigue: BIPHENTIN should not be used for the prevention or treatment of normal fatigue states.

BIPHENTIN is contraindicated with the use of Monoamine Oxidase (MAO) Inhibitors (see 2 CONTRAINDICATIONS, Co-Administration of Monoamine Oxidase Inhibitors (MAOIs)).

Caution should be exercised in prescribing concomitant drugs.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY, Genotoxicity and Carcinogenicity for discussion on animal data.

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 (see 2 CONTRAINDICATIONS).
  - 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 (see 2 CONTRAINDICATIONS).
- 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.

Dependence/Tolerance

Like other stimulants, BIPHENTIN has the potential for abuse. BIPHENTIN should be given cautiously, particularly to those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

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 withdrawal from drug use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of an underlying disorder that may require follow-up.

Driving and Operating Machinery

Because methylphenidate may affect performance, due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery. Patients should be cautioned accordingly until they are reasonably certain that BIPHENTIN does not adversely affect their ability to engage in such activities.

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.

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.

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.

- Motor and Verbal Tics, and Worsening of Tourette's Syndrome:

  CNS stimulants, including methylphenidate, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported with other CNS stimulants. It is recommended that the family history be assessed, and that the patient is clinically evaluated for tics or Tourette's syndrome before initiating methylphenidate. Regular monitoring for the emergence or worsening of tics or Tourette's syndrome during treatment with methylphenidate is recommended at every dose adjustment and every visit, and treatment discontinued if clinically appropriate (see 2 CONTRAINDICATIONS).

- Serotonin toxicity / Serotonin syndrome

  Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported with methylphenidate, including BIPHENTIN particularly during combined use with other serotonergic drugs (see 9.4 Drug-Drug Interactions, Serotonergic Drugs).

  Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g., tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

  - Spontaneous clonus
  - Inducible clonus or ocular clonus with agitation or diaphoresis
  - Tremor and hyperreflexia
  - Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

  If concomitant treatment with BIPHENTIN and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.4 Drug-Drug Interactions, Serotonin toxicity/Serotonin syndrome). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Ophthalmologic

Visual Disturbance

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported (see 8 ADVERSE REACTIONS).

Psychiatric

- 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 health professional should initiate appropriate treatment of the underlying psychiatric condition and

consider a possible change in the ADHD treatment regimen (see 8.5 Post-Market Adverse Reactions).

- Aggression, Anxiety and Agitation

  Aggressive behaviour or hostility, marked anxiety or agitation are often observed in children and adolescents with ADHD and have 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, marked anxiety or agitation.

- 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.

- 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.

- Pre-Existing Psychosis

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

- Depression

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

Reproductive Health: Female and Male Potential

- Function

  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 8.5 Post-Market Adverse 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.

- Teratogenic Risk:

  Methylphenidate hydrochloride has been shown to have teratogenic effects in rabbits when given

in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively (see 16 NON-CLINICAL TOXICOLOGY).

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.

7.1 Special Populations

7.1.1 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.

7.1.2 Breast-feeding

Case reports showed that methylphenidate was distributed into breast milk reaching a milk-to-plasma ratio of approximately 2.5 (see 10.3 Pharmacokinetics, Elimination). A risk to the suckling child cannot be excluded hence precaution should be exercised because many drugs can be excreted in human milk. 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.

7.1.3 Pediatrics

Pediatrics (<6 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in patients under 6 years of age (see 1.1 Pediatrics).

7.1.4 Geriatrics

Geriatrics (>65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use (see 1.2 Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety and efficacy of BIPHENTIN was investigated in adults (>18 years old) and children (6 to 18 years old). The most common adverse events reported in clinical trials in 10% of patients or greater were headache, decreased appetite, nervousness, insomnia, nausea, anxiety, dry mouth, somnolence and affect lability. Four serious adverse events, judged to be not related to study medication, were reported in children during clinical trials or compassionate use with BIPHENTIN: adjustment disorder with mixed disturbance of emotion and conduct (n=1), injury-induced migraine headache (n=1), appendicitis (n=1) and conversion disorder (n=1).

Although not reported during clinical trials with BIPHENTIN, sudden death has occurred in pediatric patients with structural cardiac abnormalities and other serious cardiac problems taking CNS stimulants at recommended doses for ADHD and sudden death, stroke and myocardial infarction have occurred in adults treated with CNS stimulants at recommended doses. Although not reported during clinical trials with BIPHENTIN, CNS stimulants have a high potential for abuse and dependence (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 2, which includes all events, whether considered by the clinical investigator to be related to the study drug or not.

Table 2 – Adverse Events[a] with a ≥1% Incidence in Adult Patients (>18 years of age) with ADHD Treated with BIPHENTIN

	BIPHENTIN n = 50 (%)	Placebo n = 50 (%)
General Disorders and Administration Site Conditions		
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

	BIPHENTIN n = 50 (%)	Placebo n = 50 (%)
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 effect	0.0	2.0
Gastrointestinal Disorders		
Decreased appetite	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
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

	BIPHENTIN n = 50 (%)	Placebo n = 50 (%)
Respiratory, Thoracic and Mediastinal Disorders		
Rhinitis	4.0	0.0
Cough	2.0	0.0
Pharyngitis	2.0	0.0
Epistaxis	0.0	2.0
Hiccups	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.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Adverse events in children aged 6 to 11 and adolescents aged 12 to 18 with ADHD were evaluated in two Canadian randomized controlled clinical trials of BIPHENTIN in comparison with placebo and immediate release methylphenidate. Table 3 and Table 4 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.

Table 3 – Adverse Events[a] with a ≥1% Incidence in Children (6 to 11 years of age) with ADHD Treated with BIPHENTIN

	BIPHENTIN n = 68 (%)	IR methylphenidate n = 69 (%)
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
Infections and Infestations		
Influenza	5.9	7.4
Infection	2.9	2.9
Nervous System Disorders		
Somnolence	11.8	4.4

	BIPHENTIN n = 68 (%)	IR methylphenidate n = 69 (%)
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		
Decreased appetite	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
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

	BIPHENTIN n = 68 (%)	IR methylphenidate n = 69 (%)
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.

Table 4 – Adverse Events[a] with a ≥1% Incidence in Adolescents (12 to 18 years of age) with ADHD Treated with BIPHENTIN

	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
Gastrointestinal Disorders		
Decreased appetite	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	0.0	5.0
Asthma	0.0	2.5
Sinusitis	0.0	2.5
Psychiatric Disorders		
Nervousness	27.5	25.0

	BIPHENTIN n = 40 (%)	IR methylphenidate n = 40 (%)
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.

8.3 Less Common Clinical Trial Adverse Reactions

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

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

There were no adverse events reported to have occurred in <1% of the children (6 to 11 years of age) in the BIPHENTIN clinical trials.

There were no adverse events reported to have occurred in <1% of the adolescents (12 to 17 years of age) in the BIPHENTIN clinical trials.

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

8.5 Post-Market Adverse 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 7 WARNINGS AND PRECAUTIONS,

Psychiatric, Suicidal Behaviour and Ideation).

- Adverse Events Reported with 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:

  Alopecia, angioedema, blurred vision, convulsions, dizziness, dyskinesia, erythema, flushing, hallucinations, incontinence, mydriasis, psychotic disorder, tremor, trismus, Raynaud's phenomenon, epistaxis, anaphylactic reaction, photosensitivity reaction, skin discoloration, skin odor abnormal, muscle cramps, choreoathetoid movements, presyncope, somnambulism, dysphemia, euphoric mood, visual disturbance, difficulties in accommodation, vasodilation, cardiac arrhythmias, ECG QT prolongation, change in sustained attention, dermatillomania, hallucination, impulsive behaviour, logorrhea, obsessive–compulsive disorder, onychophagia, self-injurious behaviour, thinking abnormal, aplastic anemia, pancytopenia, leucopenia, thrombocytopenia, hypoglycemia, rhabdomyolysis, transient depressed mood and priapism.

  Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate products: instances of abnormal liver function (e.g., ranging from transaminase elevation to hepatic coma); isolated cases of cerebral arteritis and/or occlusion and gynecomastia. 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.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Co-Administration of Monoamine Oxidase Inhibitors (MAOIs); see 2 CONTRAINDICATIONS 9.4 Drug-Drug Interactions, Monoamine Oxidase Inhibitors
- Co-Administration of Clonidine; see 9.4 Drug-Drug Interactions, Clonidine

9.2 Drug Interactions Overview

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

9.3 Drug-Behavioural Interactions

Alcohol

Patients undergoing BIPHENTIN therapy should be advised to avoid alcohol during treatment (see 7 WARNING AND PRECAUTIONS, Dependence/Tolerance

Alcohol may exacerbate the CNS adverse effect of BIPHENTIN. Alcohol may induce the production of methylphenidate. The amount of methylphenidate production is proportional to the blood alcohol concentration.

9.4 Drug-Drug Interactions

- Anti-hypertensive Drugs

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular

- Antipsychotics

  Because a predominant action of methylphenidate is to increase extracellular dopamine levels, BIPHENTIN may be associated with pharmacodynamic interactions when co-administered with some antipsychotics. Caution is warranted in patients receiving both BIPHENTIN and an antipsychotic, as extrapyramidal symptoms could emerge when these drugs are administered concomitantly or when adjusting the dosage of one or both drugs.

- 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.

- Vasopressor Agents

  Because of possible increases in blood pressure and heart rate, BIPHENTIN should be used cautiously with drugs with similar 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)
  - 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 (MAOIs)

  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 2 CONTRAINDICATIONS).

- Serotonergic Drugs

  The concomitant use of methylphenidate and serotonergic drugs is not recommended as this may lead to the development of serotonin syndrome on rare occasions. This includes serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), serotonin 5-HT1 receptor agonists (triptans), and 5-HT3 receptor antagonist antiemetics. If concomitant treatment with BIPHENTIN and other serotonergic agents is clinically warranted, careful observation of the patient is advised (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Toxicity / Serotonin syndrome).). If serotonin toxicity is suspected, BIPHENTIN (and serotonergic drugs) must be immediately discontinued and appropriate treatment instituted.

9.5 Drug-Food Interactions

A pharmacokinetic study demonstrated no significant differences in the rate and extent of absorption in patients under fed or fasted conditions (see 10.3 Pharmacokinetics, Absorption). BIPHENTIN may be taken with or without food. However, concomitant food intake has variable effects on methylphenidate exposure. Thus, a regular morning routine should be established, with regard to the content and timing of meals, in order to ensure consistent efficacy and safety (see 4.4, Administration) .

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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.

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.

10.2 Pharmacodynamics

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.

BIPHENTIN is a once-daily, modified-release methylphenidate preparation which utilizes multilayer release - MLR™ bead technology, where 40% of the dose is provided as an immediate release and 60% is provided through a gradual release. Data from clinical trials suggests that once-daily administration of BIPHENTIN, in the morning, improves behavioral and cognitive measures in adults and children over 6 years of age, with improvements observed within 1 hour and persisting into the evening (see 14.1 Clinical Trials by Indication, Attention-Deficit Hyperactivity Disorder (ADHD)).

10.3 Pharmacokinetics

Absorption:

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

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). Relative partial AUC was 73.67% and 97.14% for time segments 0 to 3 hours fasted and 0 to 4 hours fed, 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%). Relative partial AUC was 93.69% for the 0 to 4 hour time segment.

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.

Distribution:

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%).

Metabolism:

The primary route of metabolism for methylphenidate is de-esterification 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%).

Elimination:

Methylphenidate is excreted almost entirely in the urine. After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was ritalinic acid, accounting for approximately 80% of the dose (see 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

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).

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of BIPHENTIN has not been studied in children less that 6 years of age, and BIPHENTIN should not be used in this patient population.
- **Geriatrics:** There are no data available for the use of BIPHENTIN in patients over 65 years of age.
- **Pregnancy and Breast-feeding:** 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.
- **Hepatic Insufficiency:** BIPHENTIN has not been studied in patients with hepatic insufficiency.
- **Renal Insufficiency:** There is limited experience with the use of methylphenidate in patients with renal insufficiency. Since renal clearance is not a significant contributor to methylphenidate

elimination, and ritalinic acid is an inactive metabolite, renal insufficiency is expected to have little effect on the pharmacokinetics of BIPHENTIN.

11 STORAGE, STABILITY AND DISPOSAL

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

Keep BIPHENTIN in a safe place out of sight and reach of children and pets.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

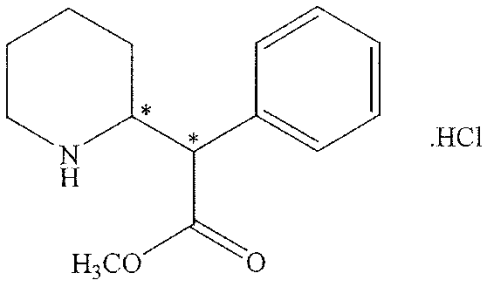
Drug Substance

Proper name: methylphenidate hydrochloride

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

Molecular formula and molecular mass: $C_{14}H_{19}NO_2HCl$, 269.77 g/mol

Structural formula:



Physicochemical properties: Methylphenidate hydrochloride is a white, odourless crystalline powder. Solutions are acidic to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. It has a pKa of 8.9 and a melting point between 224°C and 226°C.

14 CLINICAL TRIALS

14.1 Efficacy and Safety studies

Trial Design and Study Demographics

BIPHENTIN® (methylphenidate hydrochloride controlled-release capsules) was studied in four 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 5 - Summary of Patient Demographics for Clinical Trials in Children ≥6 Years of Age with ADHD

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 1 022-004	Randomized, double-blind crossover vs. IR methylphenidate	10 - 60 mg/day[a], oral, 5 to 11 weeks[b]	90	11.0 (6.4 to 17.5)	M = 74 F = 16

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 2 022-005	Randomized, double-blind crossover vs. IR methylphenidate vs. placebo	20 – 60 mg/day[c], oral, 3 weeks[d]	17*	11.3 (6.8 to 15.3)	M = 15 F = 2
Study 3 RP-BP-EF001	Randomized, double-blind crossover, analog classroom study vs. placebo	15 – 40 mg/day[e], oral, 4 to 6 weeks[f]	22	8.8 (6.0 to 12.0)	M = 12 F = 10

[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.
[c] 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).
[d] Represents 1-week on each treatment.
[e] Patients were crossed-over between BIPHENTIN and placebo at the same total daily dose, based on titration to optimal effect.
[f] Represents titration to optimal effect (two to four weeks), followed by a one-week double-blind treatment at optimal dose on active or placebo culminating in a 12-hour classroom assessment, and another one-week double-blind treatment at optimal dose on the remaining treatment (active or placebo), culminating in a second 12-hour classroom assessment.
*18 enrolled, 17 evaluable

Table 6 – Summary of Patient Demographics for Clinical Trials in Adults >18 Years of Age with ADHD

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 4 022-008	Randomized, double-blind crossover vs. placebo	10 - 80 mg/day, oral, 5 to 11 weeks[a]	50	37.2 (18.8 to 57.1)	M = 32 F = 18

[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.

14.2 Study Results

Table 7 – Results of Study 1 (022-004) in Children ≥6 Years of Age with ADHD

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
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)	

Table 8– Results of Study 2 (022-005) in Children ≥6 Years of Age with ADHD

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
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])*[b]	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)*[b] (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)*[b]	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)	

[a] 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.
[b] Improvements, relative to placebo, were noted within 1 hour on BIPHENTIN and persisted into the early evening.

Table 9 – Results of Study 3 (RP-BP-EF001) in Children ≥6 and ≤12 Years of Age with ADHD*

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
SKAMP Total Score (LS mean per item score over all postdose timepoints [hour 1 to 12])	BIPHENTIN[a] 1.32	Placebo 2.18
	(BIPHENTIN vs. placebo, p = 0.0001)	
SKAMP Total Score (LS mean per item score at each post dose time point) *[Pre-specified Key Secondary Outcome]*	BIPHENTIN[a] Hour 1 0.76 Hour 2 1.01 Hour 3 1.29 Hour 4.5 1.33 Hour 6 1.43 Hour 7.5 1.25 Hour 9 1.66 Hour 10.5 1.48 Hour 12 1.56	Placebo Hour 1 1.41 Hour 2 1.90 Hour 3 2.25 Hour 4.5 2.29 Hour 6 2.32 Hour 7.5 2.38 Hour 9 2.35 Hour 10.5 2.21 Hour 12 2.60
	(BIPHENTIN[a] vs. placebo, all p ≤ 0.05)	

*Lower SKAMP total scores indicate improvement
[a]BIPHENTIN was administered as a single, optimized, morning dose.

Table 10 – Results of Study 4 (022-008) in Adults ≥18 Years of Age with ADHD

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
Investigator Clinical Global Impressions *(Global Improvement from very much improved [1] to very much worse [7])*	BIPHENTIN[a] 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[a] vs. Placebo, p = 0.0015)	
Conners' Adult ADHD Rating Scale - Self *(ADHD Index T score)*	Baseline 72.3 ± 8.2 BIPHENTIN[a] 60.1 ± 12.7	Baseline 72.3 ± 8.2 Placebo 66.9 ± 12.5
	(BIPHENTIN[a] vs. Placebo, p = 0.0083)	
Conners' Adult ADHD Rating Scale - Observer *(ADHD Index T score)*	Baseline 73.4 ± 6.8 BIPHENTIN[a] 62.5 ± 13.4	Baseline 73.4 ± 6.8 Placebo 66.6 ± 14.1
	(BIPHENTIN[a] vs. Placebo, p = 0.1404)	

[a]BIPHENTIN was administered as a single, optimized, morning dose.

15 MICROBIOLOGY

No microbiological information is required for this product.

16 NON-CLINICAL TOXICOLOGY

Genotoxicity: Methylphenidate was not mutagenic in the Salmonella assay system. Epidemiology

studies of methylphenidate have found no evidence of a carcinogenic effect in humans.

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.

Reproductive and Developmental Toxicology: 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 is approximately 100 times and 40 times higher than the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

BIPHENTIN®

Methylphenidate hydrochloride controlled-release capsules

Read this carefully before you start taking **BIPHENTIN®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **BIPHENTIN**.

Serious Warnings and Precautions

- **Drug Dependence**
  Like other stimulants, BIPHENTIN has the potential to be abused. This can lead to you becoming dependent on BIPHENTIN or cause you to need a higher dose to have the same effect.

What is BIPHENTIN used for?

- BIPHENTIN is a once-daily treatment for Attention-Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents and adults.

BIPHENTIN is NOT recommended for use 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.

How does BIPHENTIN work?

BIPHENTIN belongs to a group of medicines called central nervous system stimulants. The way BIPHENTIN works in the brain is not completely known. 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.

What are the ingredients in BIPHENTIN?

Medicinal ingredients: methylphenidate hydrochloride.

Non-medicinal ingredients: ammonio methacrylate copolymer, type B; gelatin, hydroxpropyl 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

BIPHENTIN comes in the following dosage forms:

Controlled-release capsules: 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).

Do not use BIPHENTIN if:

- you are allergic to methylphenidate hydrochloride, any other central nervous system stimulants, or any of the other ingredients in BIPHENTIN.
- you have ever had heart problems such as a heart attack, irregular heartbeat, chest pain, heart failure, heart disease or were born with a heart problem.
- you have anxiety, tension, or agitation.
- you have glaucoma (increased eye pressure).
- you 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.
- you have moderate to severe high blood pressure.
- you have hardened arteries.
- you have an overactive thyroid gland.
- you are taking or have recently taken (in the last 14 days) any medications from a group called monoamine oxidase inhibitors. This includes phenelzine, tranylcypromine, moclobemide.
- have a history of drug abuse.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BIPHENTIN. Talk about any health conditions or problems you may have, including if you:

- have mild high blood pressure, heart problems or heart defects, such as a serious structural heart abnormality.
- have a family history of sudden cardiac death.
- have thyroid problems.
- have had seizures or abnormal EEGs (measure of brainwave activity).
- do high-intensity exercise or activities.
- have mental health problems or a family history of mental health problems, including:
  - psychosis
  - mania
  - bipolar disorder
  - depression
  - aggression
  - suicide
- drink alcohol or have a history of alcohol abuse. You should not drink alcohol while taking BIPHENTIN.
- have circulation problems in fingers and toes, including numbness, feeling cold or pain (Raynaud's phenomenon).
- are pregnant or plan to become pregnant. BIPHENTIN should not be used during pregnancy.
- are breast-feeding or plan to breast-feed. BIPHENTIN can pass through your breast milk. You should consult with your healthcare professional to determine if you should stop breast-feeding or discontinue BIPHENTIN.
- take other drugs for ADHD or depression.

Other warnings you should know about:

Driving and using machines
BIPHENTIN can affect your ability to drive and use potentially dangerous tools or machinery. You should not drive or use tools or machinery until you know how you respond to BIPHENTIN.

Dependence and tolerance

Like other stimulants, BIPHENTIN has the potential to be abused, leading to dependence and tolerance. If you have a history of drug or alcohol abuse, talk to your healthcare professional. Do not change your dose or stop taking BIPHENTIN without first talking to your healthcare professional. If you stop taking BIPHENTIN, you will need careful supervision because you may feel very depressed.

Growth in children: Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate hydrochloride in children. Your healthcare professional will carefully watch your child's height and weight. If your child is not growing or gaining weight as expected, your healthcare professional may stop treatment.

Heart-related problems
The following heart related problems have been reported in people taking medicine to treat ADHD like BIPHENTIN:

- sudden death in patients who have heart problems or heart defects, such as structural heart abnormalities.
- stroke and heart attack.
- increased blood pressure.
- increased 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 healthcare professional will check:

- you for heart problems before starting BIPHENTIN.
- your blood pressure and heart rate regularly during treatment with BIPHENTIN.

Seek immediate medical help if you have any signs of heart problems such as chest pain, difficulty breathing or fainting while taking BIPHENTIN.

Mental health problems
The following mental health problems have been reported in people taking medicine to treat ADHD like BIPHENTIN:

- new or worse thoughts or feelings related to suicide (thinking about or feeling like killing yourself) and suicide actions (suicide attempt, suicide ideation, suicide completed)
- new or worse bipolar disorder (extreme mood swings, with periods of excitement, switching between periods of sadness)
- new or worse aggressive behavior or hostility
- new psychotic symptoms (such as hearing voices, believing things that are not true, being suspicious)

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

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.

Seek immediate medical help if you have any mental health symptoms while taking BIPHENTIN.

Serotonin Syndrome

Serotonin syndrome is a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take BIPHENTIN with certain antidepressants or migraine medications.

Serotonin syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness and coma.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BIPHENTIN:

Serious Drug Interactions

Do not take BIPHENTIN if you are:

- taking or have recently taken (in the last 14 days) any MAOIs as you may have serious side effects.
- **Taking BIPHENTIN and Clonidine (used to treat high blood pressure) may cause serious side effects or sudden death.**

- alcohol – you/your child should avoid alcohol, including any medications containing alcohol, such as some cough syrups, while taking BIPHENTIN.
- certain medicines used to treat or prevent blood clots, such as warfarin.
- certain medicines used to treat seizures, such as phenobarbital, phenytoin, or primidone.
- certain medicines for depression and mood disorders, such as Tricyclic Antidepressants and Selective Serotonin Reuptake Inhibitors (SSRIs).
- certain medicines used to treat migraines.
- certain medicines used to treat nausea.
- medicines used to treat high blood pressure.
- medicines used to treat psychotic symptoms.

How to take BIPHENTIN:

- your healthcare professional will decide the dose that is right for you or your child. Always follow the directions of your healthcare professional and never change your dose or stop taking BIPHENTIN without first discussing it with your healthcare professional.
- BIPHENTIN should be taken once-a-day, with or without food, in the morning.
- a consistent morning routine should be established, with regard to the content and timing of meals.
- BIPHENTIN capsules must be swallowed whole with a full glass of water and should never be crushed or chewed.
- for patients unable to swallow the capsule, the capsule may be opened and the entire contents sprinkled onto applesauce, ice cream or yogurt. Do not sprinkle in liquids.

How to sprinkle BIPHENTIN onto food:

1. Measure a tablespoon of applesauce, ice cream or yogurt.
2. Open the capsule.
3. Sprinkle the entire contents (beads) onto the tablespoon.
4. Take the entire mixture immediately or within 30 minutes.
    - do not chew the capsule contents (beads).
    - rinse your mouth with water and swallow the water.
    - do not keep any of the food/medicine mixture for another dose.
    - throw out any food/medicine mixture if:
        - it has been more than 30 minutes since you sprinkled the capsule onto the food.
        - you do not remember when you sprinkled the capsule onto the food.
        - you do not remember which food you sprinkled the capsule onto.

Usual dose:

<u>Children/adolescents (6 – 18 years of age) and adults (>18 years of age):</u>

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

Overdose:

If you think you, or a person you are caring for, have taken too much BIPHENTIN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take your dose in the morning, wait until the next day and take the usual dose at the usual time in the morning. Do not take an afternoon dose. Do not double the dose to make up for the missed dose.

What are possible side effects from using BIPHENTIN?

These are not all the possible side effects you may have when taking BIPHENTIN. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- headache
- sleeplessness
- drowsiness
- dizziness
- nervousness
- anxiety
- irritability
- loss of appetite
- weight loss, weight gain
- stomach discomfort nausea (feeling sick), vomiting, diarrhea
- increased sweating
- dry mouth
- difficulty opening the mouth (trismus)
- lack of bladder control (incontinence)
- swelling of breast in boys and men

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Mental Health Problems: Paranoia, delusions Hallucinations: seeing, feeling or hearing things that are not real Mania: feeling unusually excited, or over-active Depression Agitation, irritability, anxiety, nervousness Aggression, hostility Compulsions		✓	
COMMON			
Heart Problems: fast heartbeat, palpitations, chest pain, difficulty breathing, fainting			✓
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or fast or uneven heartbeat.	✓		
blurred vision		✓	
UNKNOWN			
Priapism: long-lasting (greater			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
than 4 hours in duration) and painful erection of the penis			
Raynaud's Phenomenon: discolouration of the fingers and toes, pain, sensations of cold and/or numbness		✓	
Serious Allergic Reaction: itching, skin rash, swelling of the mouth, face, lips, or tongue, trouble swallowing, trouble breathing			✓
Seizures or Convulsions: loss of consciousness with uncontrollable shaking			✓
Suicidal Behaviour: thoughts or feelings about harming yourself			✓
Rhabdomyolysis (breakdown of damaged muscle): muscle weakness, muscle pain, muscle spasms, red-brown coloured urine		✓	
Bladder Infection: increased need to urinate, pain when urinating, blood in the urine		✓	
Tourette's Syndrome: motor tics (hard-to-control, repeated twitching of any part of your body) and verbal tics (hard-to-control repeating of sounds or words)			✓
Edema: swollen hands, ankles or feet	✓		
Nosebleed	✓		

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**.**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature (15°C to 30°C). Protect from moisture.
- Keep unused or expired BIPHENTIN in a secure place to prevent theft, misuse, or accidental exposure.
- Keep out of reach and sight of children and pets.

If you want more information about BIPHENTIN:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.elvium.ca, or by calling 1-800-744-0005.

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