PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

QUILLIVANT® ER Oral Suspension

Methylphenidate Hydrochloride Extended-Release Powder for Oral Suspension

300 mg, 600 mg, 750 mg and 900 mg/bottle

300 mg/60 mL, 600 mg/120 mL, 750 mg/150 mL and 900 mg/180 mL (5 mg/mL) when reconstituted

QUILLIVANT® ER Chewable Tablets

Methylphenidate Hydrochloride Extended-Release Chewable Tablets

20 mg, 30 mg, and 40 mg

QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets are not interchangeable

Central Nervous System Stimulant

KYE Pharmaceuticals Inc.

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Suites 302 & 302A

Mississauga, ON, Canada

L5N 2X7

Date of Initial Authorization:

September 20, 2023

Submission Control Number: 243224

RECENT MAJOR LABEL CHANGES

INITIAL

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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

QUILLIVANT® ER Oral Suspension (methylphenidate hydrochloride extended-release powder for oral suspension) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in:

- Children (6-12 years of age)

QUILLIVANT® ER Chewable Tablets (methylphenidate hydrochloride extended-release chewable tablets) are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in:

- Children (6-12 years of age)

Long-Term Use

The effectiveness of QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets for long-term use has not been systematically evaluated for more than two weeks and 1 week, respectively, in placebo-controlled trials. Therefore, the physician who elects to use QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Need for Comprehensive Treatment Program

QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets are indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Drug treatment is not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential in children and adolescents with this diagnosis and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

1.1 Pediatrics

Pediatrics (< 6 years of age): QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets should not be used in children under six years. 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.

Pediatrics (6-12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets in pediatric patients aged 6-12 years has been established. Therefore, Health Canada has authorized an indication for pediatric use (see 4.2 Recommended Dose and Dosage Adjustment).

Pediatrics (13-17 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets in pediatric patients aged 13-17 years has not been established; therefore, Health Canada has not authorized an indication for use in ages 13-17 years.

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

QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets are 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. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other methylphenidate products (see 8 ADVERSE REACTIONS). For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING. Additionally, QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets are contraindicated in patients with the following:

- Known hypersensitivity or idiosyncrasy to the sympathomimetic amines
- Thyrotoxicosis
- Advanced arteriosclerosis
- Symptomatic cardiovascular disease
- Moderate to severe hypertension
- Glaucoma
- History of drug abuse
- During or within 14-days following the administration of monoamine oxidase inhibitors (hypertensive crises may result) (see 9 DRUG INTERACTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Drug Dependence – Like other stimulants, QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets have 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

- QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets 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 CONTRAINDICATIONS 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.
- Prior to treating children with CNS stimulants including QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets, assess for the presence of cardiac disease (i.e., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) (see

WARNINGS AND PRECAUTIONS).

- Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and periodically re-evaluate the need for QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets use (see SERIOUS WARNINGS AND PRECAUTIONS BOX, WARNINGS AND PRECAUTIONS).
- QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets 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 QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets varies widely (see 4.2 Recommended Dose and Dosage Adjustment).
- If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug. QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets should be periodically discontinued to assess the child's condition. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.
- Pharmacologic treatment of ADHD may be needed for extended periods. Health care providers should periodically re-evaluate the long-term use of QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets, and adjust dosage as needed.
- Patients who are considered to need extended treatment with QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets should undergo periodic evaluation of their cardiovascular status (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).
- Patients should be advised to avoid alcohol while taking QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets.
- QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets are not interchangeable (see Recommended Dose and Dosage Adjustment)

4.2 Recommended Dose and Dosage Adjustment

QUILLIVANT® ER Oral Suspension:

- Before administering the dose, VIGOROUSLY SHAKE the bottle of QUILLIVANT® ER Oral Suspension for at least 10 seconds, to ensure that the proper dose is administered.
- The recommended starting dose of QUILLIVANT® ER Oral Suspension for patients 6-12 years is 20 mg once daily in the morning. The dose may be titrated up or down weekly in increments of 10 mg or 20 mg. Daily doses above 60 mg have not been studied and are not recommended. As with any CNS stimulant, during titration of QUILLIVANT® ER Oral Suspension, the prescribed dose should be adjusted, if necessary, until a well-tolerated, therapeutic dose is achieved.
- Patients that are unable to tolerate the minimum dose of 20 mg should not take this medication

QUILLIVANT® ER Chewable Tablets:

- The recommended starting dose of QUILLIVANT® ER Chewable Tablets for patients 6-12 years is 20 mg once daily orally in the morning. The dose may be titrated up or down weekly in increments of 10 mg, 15 mg, or 20 mg. The 10 mg and 15 mg doses can each be achieved by breaking in half

the functionally scored 20 mg and 30 mg tablets, respectively. Daily doses above 60 mg have not been studied and are not recommended. As with any CNS stimulant, during titration of QUILLIVANT® ER Chewable Tablets, the prescribed dose should be adjusted, if necessary, until a well-tolerated, therapeutic dose is achieved.

- Patients that are unable to tolerate the minimum dose of 20 mg should not take this medication

If switching from other methylphenidate products, including switching from QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets or vice versa, discontinue that treatment, and titrate with QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets using the above titration schedule.

Do not substitute for other methylphenidate products on a milligram-per-milligram basis, because of different methylphenidate base compositions and differing pharmacokinetic profiles (see CLINICAL PHARMACOLOGY).

4.3 Reconstitution

QUILLIVANT® ER Oral Suspension is supplied as a powder for oral suspension which must be reconstituted with water by the pharmacist prior to dispensing. Preparation instructions: Tap bottle until powder flows freely. Remove bottle cap and add specified amount of water to the bottle (see

Table 1). Fully insert bottle adapter into neck of bottle (

Figure 1). Replace bottle cap. Shake with vigorous back and forth motion for at least 10 seconds to prepare suspension.

Figure 1: Bottle Adapter Insertion

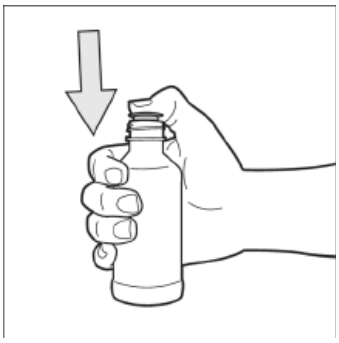


Table 1: QUILLIVANT® ER Oral Suspension Product Reconstitution Instructions - 5 mg/mL

Amount of drug in bottle	Amount of water to add to bottle	Final reconstituted volume (yield)
300 mg	53 mL	60 mL
600 mg	105 mL	120 mL
750 mg	131 mL	150 mL
900 mg	158 mL	180 mL

Store reconstituted QUILLIVANT® ER Oral Suspension at 15 to 30ºC. Dispense in original packaging (bottle in carton) with bottle adapter inserted and with enclosed oral dosing dispenser. QUILLIVANT® ER Oral Suspension is stable for up to 4 months after reconstitution.

4.4 Administration

QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets should be orally administered once daily in the morning with or without food (see 10 CLINICAL PHARMACOLOGY).

4.5 Missed Dose

If a dose of QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets 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 methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: agitation, cardiac arrhythmias, confusion, convulsions (may be followed by coma), delirium, euphoria, flushing, hallucinations, headache, hyperpyrexia, hyperreflexia, hypertension, muscle twitching, mydriasis and dryness of mucus membranes, rhabdomyolysis, palpitations, sweating, tachycardia, tremors and vomiting.

Management consists of providing supportive measures. The patient must be protected against self-injury and against external stimuli that would exacerbate overstimulation already present. 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 prolonged release of methylphenidate from QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets should be considered when treating patients with overdose. Alcohol may induce the production of ethylphenidate. The amount of ethylphenidate production is proportional to the blood alcohol concentration (see 9.2 Drug Interactions Overview). 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 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Extended-Release Powder for Oral Suspension 300 mg, 600 mg, 750 mg, and 900 mg/bottle (before reconstitution): 5 mg/mL after reconstitution	anhydrous citric acid, anhydrous trisodium citrate, banana flavour, corn starch, poloxamer 188, polyvinyl acetate, povidone, silicone dioxide, sodium benzoate, sodium polystyrene sulfonate, sucralose, sucrose, talc, triacetin, xanthan gum
oral	Extended-Release Chewable Tablets 20 mg, 30 mg, and 40 mg	aspartame, cherry flavor, citric acid, crospovidone, D&C red #30 (for 30 mg strength), D&C red #7 (for 40 mg strength), guar gum, magnesium stearate, mannitol, maltodextrin, microcrystalline cellulose, polyethylene glycol 3350, polysorbate 80, polyvinyl acetate, polyvinyl alcohol, povidone, silicon dioxide, sodium lauryl sulfate, sodium polystyrene sulfonate, talc, triacetin, xanthan gum

QUILLIVANT® ER Oral Suspension is supplied as powder that, after reconstitution with water, forms an extended-release oral suspension. QUILLIVANT® ER Oral Suspension contains approximately 20% immediate-release and 80% extended-release methylphenidate (present as methylphenidate ionically-bound to the sulfonate groups of sodium polystyrene sulfonate particles). The product is supplied in a carton. Each carton also contains one bottle, one oral dosing dispenser, and one bottle adapter.

The product must be reconstituted only by the pharmacist and not by the patient or caregiver. After reconstitution, the product is a light beige to tan viscous suspension containing the equivalent of 5 mg per mL of methylphenidate hydrochloride.

QUILLIVANT® ER Chewable Tablets is supplied as a speckled capsule-shaped coated tablet containing 20 mg, 30 mg, or 40 mg of methylphenidate hydrochloride. The dosage strengths are expressed in terms of methylphenidate hydrochloride equivalents; however, only 15% of methylphenidate is

present as methylphenidate hydrochloride salt. The remaining 85% is present as methylphenidate ionically-bound to the sulfonate groups of sodium polystyrene sulfonate particles. QUILLIVANT® ER Chewable Tablets contains approximately 30% immediate-release and 70% extended-release methylphenidate. QUILLIVANT® ER Chewable Tablets 20 mg tablets are off-white and debossed with "NP 12" on one side and functionally scored on the other side. QUILLIVANT® ER Chewable Tablets 30 mg tablets are light pink and debossed with "NP 13" on one side and functionally scored on the other side. QUILLIVANT® ER Chewable Tablets 40 mg tablets are dark pink to peach and debossed with "NP 14" on one side and plain (not scored) on the other side. The tablets are supplied in bottles of 100.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

General

- 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 QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets should depend on the health professional's assessment of the chronicity and severity of the patient's symptoms. 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.
- All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: a) are involved in strenuous exercise or activities, b) use other sympathomimetic ADHD drugs or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment, a personal and family history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during ADHD treatment should undergo a prompt cardiac evaluation.
- Phenylalanine can be harmful to patients with phenylketonuria (PKU). QUILLIVANT® ER Chewable Tablets contain phenylalanine, a component of aspartame. Each 20 mg, 30 mg, and 40 mg extended-release chewable tablet contains 3 mg, 4.5 mg, and 6 mg phenylalanine, respectively. Before prescribing QUILLIVANT® ER Chewable Tablets in patients with PKU, consider the combined daily amount of phenylalanine from all sources, including QUILLIVANT® ER Chewable Tablets.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY section.

Cardiovascular

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

  Children and Adolescents:

Sudden death has been reported in association with stimulant drugs used for ADHD treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious cardiac problems. Although some serious heart problems alone carry an increased risk of sudden death, QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets 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:**

  Central Nervous System (CNS) stimulants should be used with caution in patients with a pre-existing cardiovascular or cerebrovascular condition, taking into account risk predictors for these conditions. Patients should be screened for pre-existing or underlying cardiovascular or cerebrovascular conditions before initiation of treatment with 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.

  Sympathomimetic medications cause a modest mean increase in blood pressure (about 2 to 4 mmHg) and heart rate (about 3 to 6 bpm) but individuals may have larger increases. In the placebo-controlled study of QUILLIVANT® ER Oral Suspension there were increases of up to 3.5 mmHg in systolic blood pressure, 6.0 mmHg in diastolic blood pressure, and 9.3 bpm in heart rate. In the placebo-controlled study QUILLIVANT® ER Chewable Tablets there were increases up to 7.0 mmHg in systolic blood pressure, 5.4 mmHg in diastolic blood pressure, and 11.6 bpm in heart rate added} While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure (see CONTRAINDICATIONS and DRUG INTERACTIONS).

- **Misuse and Serious Cardiovascular Adverse Events:**

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

- **Peripheral Vasculopathy, Including Raynaud's Phenomenon:**

  Stimulants used to treat ADHD, including methylphenidate products, 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.

Dependence/Tolerance

QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets should be given cautiously to patients, particularly to those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially with parenteral abuse.

Careful supervision is required during withdrawal from abuse since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of an underlying disorder that may require follow-up.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery. Stimulants may impair the ability of the patient to operate potentially hazardous machinery or vehicles. Patients should be cautioned accordingly until they are reasonably certain that QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets 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 and adolescents 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, haematological 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, in patients 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. In the presence of seizures or suspected seizures, 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.

- **Serotonin toxicity / Serotonin syndrome:**

  Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with methylphenidate, including QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets, with concomitant use of serotonergic or dopaminergic drugs (see 9.4 Drug-Drug Interactions, Serotonergic Drugs). Serotonin toxicity is characterized 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 QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets 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, Serotonergic Drugs). If serotonin toxicity is suspected, discontinuation of QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets and other serotonergic agents should be considered and appropriate treatment instituted.

Ophthalmologic

- **Increased intraocular pressure and glaucoma**

  There have been reports of elevation of intraocular pressure (IOP) and glaucoma associated with methylphenidate treatment. QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets are contraindicated in patients with glaucoma (see 2 CONTRAINDICATIONS).

- **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

- **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 or 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 patients exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

- **Aggression, Anxiety and Agitation**

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

  Aggressive behaviour, marked anxiety or agitation are often observed in patients 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, marked anxiety, or agitation.

- **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 for patients treated with ADHD drugs that caregivers and physicians monitor 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 8.5 Post-Market Adverse Reactions).

- **Depression:**

  QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets 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.

7.1 Special Populations

7.1.1 Pregnant Women

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

Studies to establish safe use of methylphenidate in pregnant women have not been conducted. Therefore, QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets should not be given to pregnant women unless the potential benefit outweighs the risk to the fetus.

- **Embryo/Fetal/Neonatal Adverse Reactions**

  CNS stimulant medications, such as QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets, can cause vasoconstriction and thereby decrease placental perfusion. Premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

7.1.2 Breast-feeding

A study conducted in rats indicated that the distribution profiles of methylphenidate in milk and plasma are similar. Case reports showed that methylphenidate was distributed into breast milk reaching a milk-to-plasma ratio of approximately 2.7 (see 10.3 Pharmacokinetics, Special Populations and Conditions, Pregnancy and Breast-Feeding). 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. A risk to the suckling child cannot be excluded. A decision should be made whether to abstain from breast-feeding or to abstain from QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman.

Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

7.1.3 Pediatrics

Pediatrics (<6 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

Pediatrics (6 – 12 years of age): Long-term effects QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets have not been well established beyond {8 weeks} and {7 weeks}, respectively.

Adolescents (13 – 17 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets in adolescent patients has not been established; therefore, Health Canada has not authorized an indication for adolescent use.

7.1.4 Geriatrics

QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets have not been studied in patients over the age of 65 years; therefore, Health Canada has not authorized an indication for geriatric use (see 1.2 Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In the QUILLIVANT® ER Oral Suspension controlled study in children with ADHD, there were 3 subjects that experienced severe treatment-emergent adverse events (affect lability, aggression and initial insomnia) and 2 subjects that had adverse events that led to discontinuation during the open-label dose optimization phase. The most common adverse event (≥5%) during the open-label phase was decreased appetite. During the double-blind phase, there were no severe treatment-emergent adverse events or adverse events that led to discontinuation. There were no serious adverse events in the study. The most common adverse event (≥5%) during the double-blind phase was affect lability.

In the QUILLIVANT® ER Chewable Tablets controlled study in children with ADHD, there were 2 subjects that had adverse events that led to discontinuation during the open-label phase. The most common adverse event (≥5%) during the open-label phase was decreased appetite. During the double-blind phase, there were no adverse events that led to discontinuation. There were no severe or serious adverse events in the study. The most common adverse event (≥5%) during the double-blind phase was upper respiratory tract infection, which was reported at a similar rate in the placebo group.

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.

The clinical trial program for QUILLIVANT® ER Oral Suspension included a total of 114 subjects including 44 pediatric (aged 6-12 years) ADHD patients in an 8 week, placebo-controlled, phase 3 double-blind classroom study. The clinical trial program for QUILLIVANT® ER Chewable Tablets included a total of 149 subjects including 90 pediatric (aged 6-12 years) ADHD patients in a 7 week, placebo-controlled, phase 3 double-blind classroom study.

The information included in this section is based on data from these studies. Adverse reactions were assessed by collecting adverse events (AEs), results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event (TEAE) of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse events observed with QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets treatment mainly reflect side effects commonly associated with methylphenidate use. Very common AEs reported by patients treated with QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets were: headache, insomnia, decreased appetite and abdominal pain. Most of the events were mild or moderate in severity.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Serious Adverse Events and Adverse Events Leading to Discontinuation of Treatment:

- **Children (6 to 12 years of age)**
    - **QUILLIVANT ER® Oral Suspension**

      In a placebo-controlled trial in children, during the double-blind treatment period, there were no discontinuations due to AEs or serious adverse events (SAEs) reported. During the open-label period, 4.4% (2/45) of QUILLIVANT® ER Oral Suspension-treated patients discontinued treatment due to AEs; one subject (2.2%) with severe affect lability and one subject (2.2%) with severe aggression. There were no SAEs reported.

    - **QUILLIVANT ER® Chewable Tablets**

      In a placebo-controlled trial in children, during the double-blind treatment period, there were no discontinuations due to AEs or serious adverse events (SAEs) reported. During the open-label period, 2.2% (2/90) of QUILLIVANT® ER Chewable Tablets-treated patients discontinued treatment due to AEs; one subject (1.1%) with moderate dysgeusia and one subject (1.1%) with decreased appetite. There were no SAEs reported.

There is limited experience with QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets in controlled trials. TEAEs reported in controlled trials in children with ADHD treated with QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets with an incidence greater or equal to 1% are presented in the tables below.

Table 3: Quillivant® ER Oral Suspension: Treatment-Emergent Adverse Events Reported by ≥1% of Children (6 to 12 years of age) with ADHD in a Laboratory Classroom Study with up to 6 weeks Open Label Titration followed by a 2 week Double Blind, Placebo-Controlled Crossover Treatment Phase*

Preferred Term	Open Label Phase (up to 6 weeks) N = 45 N (%)	Double-Blind Crossover Phase (2 weeks)	
		Placebo N = 45 N (%)	QUILLIVANT ER® Oral Suspension N = 45 N (%)
Metabolism and nutrition disorders			
Decreased appetite	25 (55.6)	0 (0.0)	1 (2.2)
Psychiatric disorders			
Affect lability	12 (26.7)	1 (1.2)	4 (8.9)
Aggression	0 (0.0)	1 (2.2)	0 (0.0)
Initial insomnia	9 (20.0)	0 (0.0)	1 (2.2)
Insomnia	8 (17.8)	0 (0.0)	0 (0.0)
Logorrhoea	4 (8.9)	0 (0.0)	0 (0.0)
Aggression	3 (6.7)	1 (1.2))	0 (0.0)
Change in sustained attention	2 (4.4)	0 (0.0)	0 (0.0)
Nail picking	2 (4.4)	0 (0.0)	0 (0.0)
Attention deficit/hyperactivity disorder	1 (2.2)	0 (0.0)	0 (0.0)
Bruxism	1 (2.2)	0 (0.0)	0 (0.0)
Depressed mood	1 (2.2)	0 (0.0)	0 (0.0)
Social avoidant behaviour	1 (2.2)	0 (0.0)	0 (0.0)
Stereotypy	0 (0.0)	1 (2.2)	0 (0.0)
Tic	0 (0.0)	0 (0.0)	1 (2.2)
Gastrointestinal disorders			
Abdominal pain upper	18 (40.0	1 (2.2)	1 (2.2)
Diarrhoea	2 (4.4)	0 (0.0)	0 (0.0)
Nausea	2 (4.4)	0 (0.0)	0 (0.0)
Vomiting	2 (4.4)	0 (0.0)	1 (2.2)
Dry Mouth	1 (2.2)	0 (0.0)	0 (0.0)
Nervous system disorders			
Headache	7 (15.6)	0 (0.0)	0 (0.0)
Dizziness	3 (6.7)	0 (0.0)	0 (0.0)
Dizziness postural	1 (2.2)	0 (0.0)	0 (0.0)
Lethargy	1 (2.2)	0 (0.0)	0 (0.0)
Mental impairment	1 (2.2)	0 (0.0)	0 (0.0)
Oromandibular dystonia	1 (2.2)	0 (0.0)	0 (0.0)
General disorders and administration site conditions			
Irritability	6 (13.3)	0 (0.0)	0 (0.0)
Fatigue	4 (8.9)	0 (0.0)	0 (0.0)
Vascular disorders			
Flushing	2 (4.4)	0 (0.0)	0 (0.0)
Cardiac disorders			
Palpitations	1 (2.2)	0 (0.0)	0 (0.0)

Preferred Term	Open Label Phase (up to 6 weeks) N = 45 N (%)	Double-Blind Crossover Phase (2 weeks)	
		Placebo N = 45 N (%)	QUILLIVANT ER® Oral Suspension N = 45 N (%)
Ear and labyrinth disorders			
Motion sickness	1 (2.2)	0 (0.0)	1 (2.2)
Eye disorders			
Vision blurred	1 (2.2)	0 (0.0)	0 (0.0)
Eye pain	0 (0.0)	0 (0.0)	1 (2.2)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	1 (2.2)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders			
Pruritus	1 (2.2)	0 (0.0)	0 (0.0)

* Study Duration: up to 8 weeks. Treatment period, including 4-6 weeks open-label dose titration (initial dose 20 mg titrated weekly in 10 or 20 mg increments until an optimal dose or the maximum dose of 60 mg/day was reached) followed by 2 weeks of stable dosing with QUILLIVANT ER® Oral Suspension or placebo administered in a randomized crossover fashion such that each patient received QUILLIVANT ER® Oral Suspension during one week and placebo during the other week.

Table 4: Quillivant® ER Chewable Tablets: Treatment-Emergent Adverse Events Reported by ≥1% of Children (6 to 12 years of age) with ADHD in a Laboratory Classroom Study with up to 6 weeks Open Label Titration followed by a 1 week Double Blind, Placebo-Controlled Treatment Phase*

Preferred Term	Open Label Phase (up to 6 weeks) N = 90 N (%)	Double-Blind Phase (1 week)	
		Placebo N = 44 N (%)	QUILLIVANT ER® Chewable Tablets N = 42 N (%)
Metabolism and nutrition disorders			
Decreased appetite	33 (36.7)	0 (0.0)	1 (2.4)
Psychiatric disorders			
Mood swings	12 (13.3)	0 (0.0)	0 (0.0)
Insomnia	10 (11.1)	0 (0.0)	0 (0.0)
Initial insomnia	4 (4.4)	0 (0.0)	0 (0.0)
Tic	3 (3.3)	0 (0.0)	0 (0.0)
Middle insomnia	2 (2.2)	0 (0.0)	0 (0.0)
Anger	1 (1.1)	0 (0.0)	0 (0.0)
Change in sustained attention	1 (1.1)	0 (0.0)	0 (0.0)
Onychophagia	1 (1.1)	0 (0.0)	0 (0.0)
Gastrointestinal disorders			
Abdominal pain upper	10 (11.1)	0 (0.0)	0 (0.0)
Dry mouth	3 (3.3)	0 (0.0)	0 (0.0)
Nausea	3 (3.3)	0 (0.0)	1 (2.4)
Abdominal pain	2 (2.2)	0 (0.0)	0 (0.0)
Vomiting	2 (2.2)	0 (0.0)	0 (0.0)
Diarrhoea	1 (1.1)	0 (0.0)	0 (0.0)
Dyspepsia	1 (1.1)	0 (0.0)	0 (0.0)
Flatulence	1 (1.1)	0 (0.0)	0 (0.0)
Nervous system disorders			
Dysgeusia	8 (8.9)	0 (0.0)	0 (0.0)
Headache	3 (3.3)	0 (0.0)	0 (0.0)
Lethargy	2 (2.2)	0 (0.0)	0 (0.0)
Dizziness	1 (1.1)	0 (0.0)	0 (0.0)
Psychomotor hyperactivity	1 (1.1)	0 (0.0)	0 (0.0)
Somnolence	1 (1.1)	0 (0.0)	0 (0.0)
General disorders and administration site conditions			
Irritability	11 (12.2)	0 (0.0)	0 (0.0)
Fatigue	2 (2.2)	0 (0.0)	0 (0.0)
Feeling jittery	2 (2.2)	0 (0.0)	0 (0.0)
Cardiac disorders			
Tachycardia	2 (2.2)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders			
Tinnitus	2 (2.2)	0 (0.0)	0 (0.0)
Eye disorders			
Dry eye	1 (1.1)	0 (0.0)	0 (0.0)

Preferred Term	Open Label Phase (up to 6 weeks) N = 90 N (%)	Double-Blind Phase (1 week)	
		Placebo N = 44 N (%)	QUILLIVANT ER® Chewable Tablets N = 42 N (%)
Excessive eye blinking	1 (1.1)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders			
Night sweats	1 (1.1)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders			
Epistaxis	1 (1.1)	0 (0.0)	0 (0.0)
Investigations			
Blood pressure systolic increased Weight decreased	1 (1.1) 0 (0.0)	0 (0.0) 0 (0.0)	0 (0.0) 1 (2.4)
Renal and urinary disorders			
Enuresis	0 (0.0)	1 (2.3)	0 (0.0)

* Study Duration: up to 7 weeks. Treatment period, including 6 weeks open-label dose titration (initial dose 20 mg titrated weekly in 10 or 20 mg increments until an optimal dose or the maximum dose of 60 mg/day was reached) followed by 1 week of stable dosing with QUILLIVANT ER® Chewable Tablets or placebo administered in a double-blind fashion such that each patient received either QUILLIVANT ER® Chewable Tablets or placebo for one week.

Additional Treatment-Emergent Adverse Events Reported During Clinical Trials with Other Methylphenidate Products

Commonly reported (≥2% of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: appetite decreased, dyspepsia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis,

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, Suicidal Behaviour and Ideation)

- **Adverse Events Reported with Methylphenidate Hydrochloride Products**

The following adverse reactions have been identified during post approval use of methylphenidate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are as follows:

Blood and Lymphatic System Disorders: Aplastic anemia, Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura

Cardiac Disorders: Angina pectoris, Arrhythmia, Bradycardia, Extrasystole, Myocardial infarction, Supraventricular tachycardia, Ventricular extrasystole

Eye Disorders: Diplopia, Mydriasis, Visual impairment

Gastrointestinal Disorders: Constipation, Diarrhea, Pancreatitis

General Disorders and Administration Site Conditions: Chest pain, Chest discomfort, Hyperpyrexia

Hepatobiliary Disorders: Acute hepatic failure, Hepatocellular injury, Severe hepatocellular injury

Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions, and Exanthemas NEC

Investigations: Alkaline phosphatase increased, Bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal

Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis, Trismus

Nervous System Disorders: Cerebrovascular accident, Cerebrovascular disorder (including Cerebral vasculitis, Cerebral hemorrhage, Cerebral arteritis, Cerebral vascular occlusion), Convulsion, Dyskinesia, Grand mal convulsion, Serotonin syndrome in combination with serotonergic drugs.

Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Libido changes, Mania, Complete Suicide, Suicide ideation, Suicide attempt, Psychotic disorder, Logorrhea, Libido disorder

Reproductive System and Breast Disorders: Gynecomastia, Priapism

Skin and Subcutaneous Tissue Disorders: Alopecia, Dermatitis exfoliative, Erythema

Vascular Disorders: Raynaud's phenomenon

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; abdominal pain; and weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, e.g., hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; and a few instances of scalp hair loss. There have been reports of serotonin syndrome following coadministration of methylphenidate with serotonergic drugs. 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.

Although a definite causal relationship has not been established, the following have been

reported in patients taking other methylphenidate products: instances of abnormal liver function, (e.g., hepatic coma); isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; and a few instances of scalp hair loss. Very rare reports of Stevens-Johnson syndrome and neuroleptic malignant syndrome (NMS) have been received. In most of the NMS cases, 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.

Priapism and Raynaud's phenomenon have also been reported with methylphenidate products.

9 DRUG INTERACTIONS

9.1 Serious drug interactions

Serious Drug Interactions
• Co-Administration of Monoamine Oxidase Inhibitors (MAOIs); see **Error! Reference source not found.**, **Error! Reference source not found.**, Monoamine Oxidase Inhibitors (MAOIs)
• Co-Administration of Clonidine; see **Error! Reference source not found.**, Clonidine

9.2 Drug Interactions Overview

Because of possible increases in blood pressure and heart rate, QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets should be used cautiously with drugs with similar pharmacological actions.

Patients should be advised not to consume alcohol while taking QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets.

Downward dose adjustment of anticoagulants, anticonvulsants and some antidepressants may be required when given concomitantly with methylphenidate.

Do not administer QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets concomitantly with monoamine oxidase inhibitors (MAOIs) or within 14 days after discontinuing MAOI treatment.

Serious adverse events including sudden death have been reported in concomitant use with clonidine.

9.3 Drug-Behavioural Interactions

- **Alcohol**

  The concomitant use of alcohol should be avoided (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance).

  Alcohol may exacerbate the CNS-related adverse effects of psychoactive drugs. Therefore, patients undergoing QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets therapy should be advised to avoid alcohol during treatment.

An in vitro study was conducted to explore the effect of alcohol on the release characteristics of methylphenidate from QUILLIVANT® ER Oral Suspension. At alcohol concentrations of 5% and 10%, there was no effect of alcohol on the release characteristics of methylphenidate. At 20% alcohol concentration, there was on average a 20% increase in drug exposure.

At 40% alcohol concentration, there was about 90% release methylphenidate from QUILLIVANT® ER Chewable Tablets 40 mg tablet within half an hour. The results with the 40 mg chewable tablet strength are considered representative of the other available tablet strengths.

9.4 Drug-Drug Interactions

- **Vasopressor Agents**

  Because of possible increases in blood pressure, QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets should be used cautiously with vasopressor agents (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypertension and Other Cardiovascular Conditions).

- **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 (e.g., tricyclics, SSRIs). 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 MAOIs and also within a minimum of 14 days following discontinuation of a MAOI (hypertensive crises may result). The same precautions apply to QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets (see 2 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.

- **Anti-Hypertensive Drugs**

  Methylphenidate products may decrease the effectiveness of drugs used to treat hypertension (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypertension and Other Cardiovascular Conditions).

- **Antipsychotics**

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

- **Serotonergic Drugs**

  There have been reports of serotonin syndrome with methylphenidate, including QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets with concomitant use of serotonergic drugs. If concomitant treatment with QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets 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, QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets (and serotonergic drugs) must be immediately discontinued and appropriate treatment instituted.

9.5 Drug-Food Interactions

Interactions with food have not been established.

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 HCl is a central nervous system (CNS) stimulant. The pharmacological properties of methylphenidate are similar to those of the amphetamines. However, in contrast to amphetamines, methylphenidate has more prominent effects on mental than motor activities. The mode of action of stimulants in 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. Methylphenidate increases extracellular concentrations of dopamine and norepinephrine by inhibiting their neuronal reuptake, and is also an MAO. 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.

Methylphenidate is a racemic mixture comprised of the d- and l-threo isomers. The d-isomer is more pharmacologically active than the l-isomer. 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. The mode of therapeutic action in ADHD is not known. Methylphenidate blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increases the release of these monoamines into the extraneuronal space.

QUILLIVANT® ER Oral Suspension contains approximately 20% immediate-release and 80% extended-release methylphenidate (present as methylphenidate ionically-bound to the sulfonate groups of sodium polystyrene sulfonate particles).

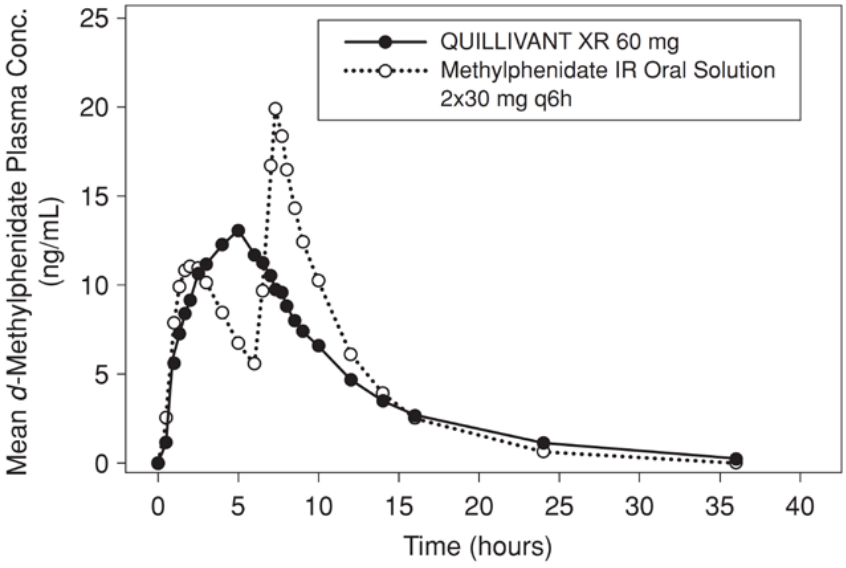
QUILLIVANT® ER Chewable Tablets contain approximately 30% immediate-release and 70% extended-release methylphenidate. The dosage strengths are expressed in terms of methylphenidate hydrochloride equivalents; however, only 15% of methylphenidate is present as methylphenidate hydrochloride salt. The remaining 85% is present as methylphenidate ionically-bound to the sulfonate groups of sodium polystyrene sulfonate particles.

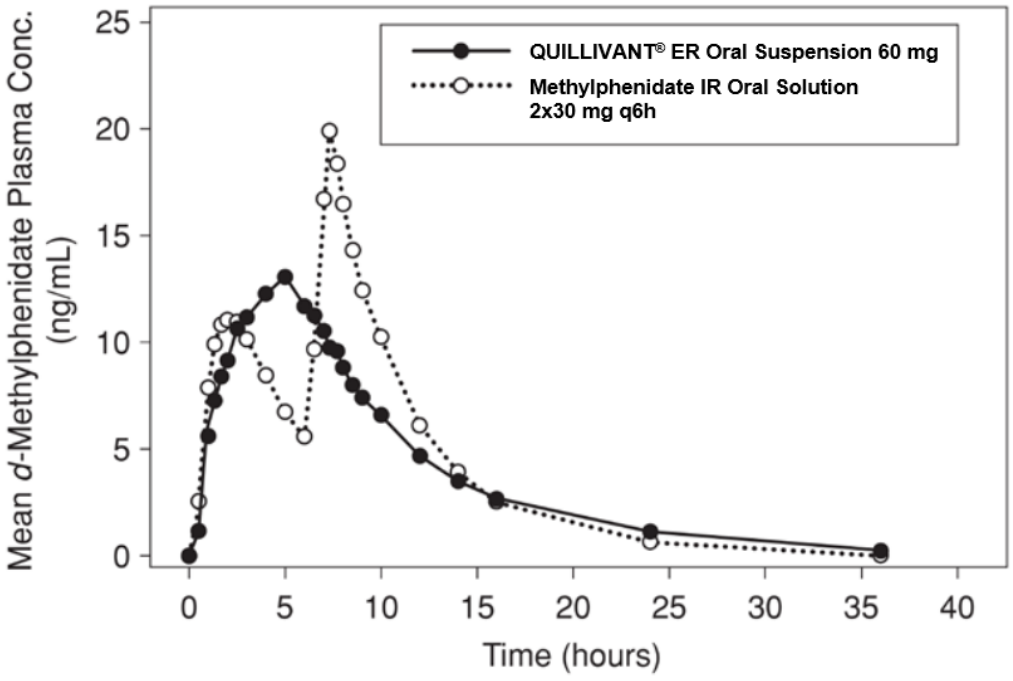
10.3 Pharmacokinetics

Absorption: Following a single, 60 mg oral dose of QUILLIVANT® ER Oral Suspension in 28 healthy adult subjects in a crossover study under fasting conditions, d-methylphenidate (d-MPH) mean (± SD) peak plasma concentrations of 13.6 (± 5.8) ng/mL occurred at a median time of 5.0 hours after dosing (

Figure **2**). The relative bioavailability of QUILLIVANT® ER Oral Suspension compared to Methylphenidate IR oral solution (2x30 mg, q6h) is 95%.

Figure 2: Mean d-Methylphenidate Plasma Concentration-Time Profiles





The single dose pharmacokinetics of d-MPH under fed conditions are summarized below from studies in children and adolescents with ADHD and healthy adults following an oral dose of 60 mg QUILLIVANT® ER.

Table 5: d-MPH PK Parameters (mean ±SD) after 60 mg QUILLIVANT® ER Oral Suspension

PK Parameter	Children† (n=3)	Adolescent† (n=4)	Adult (n=27)
T_{max} (hr)‡	4.05 (3.98-6.0)	2.0 (1.98-4.0)	4.0 (1.3-7.3)
$T_{1/2}$ (hr)	5.2±0.1	5.0±0.2	5.2±1.0
C_{max} (ng/mL)	34.4±14.0	21.1±5.9	17.0±7.7
AUC_{inf} (hr*ng/mL)	378±175	178±54.2	163.2±80.3
Cl (L/hr/kg)	4.27±0.70	5.06±1.42	5.66±2.15

* Breakfast was given 30 min prior to drug administration

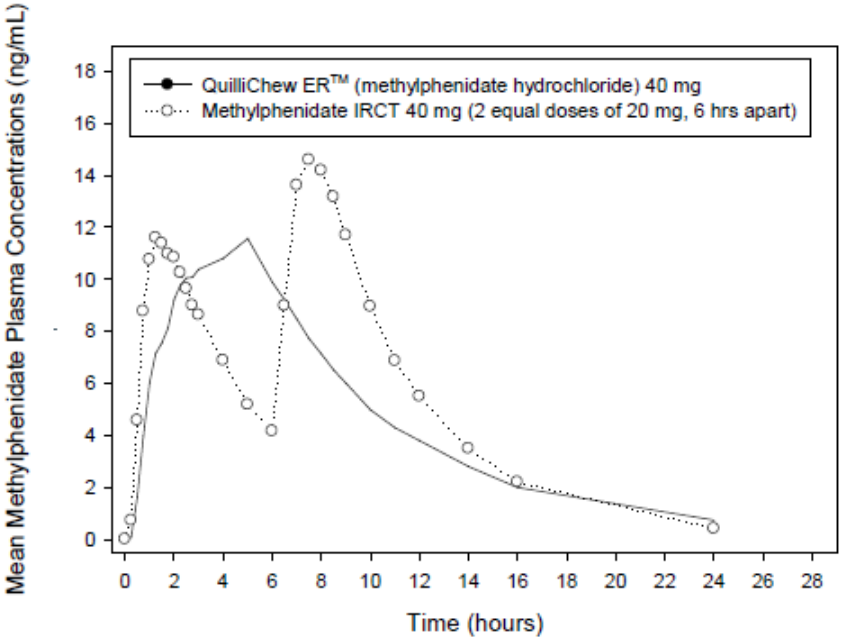
† total MPH measured in children (9-12 years old) and adolescents (13-15 years old), l-MPH <2% of d-MPH in circulation

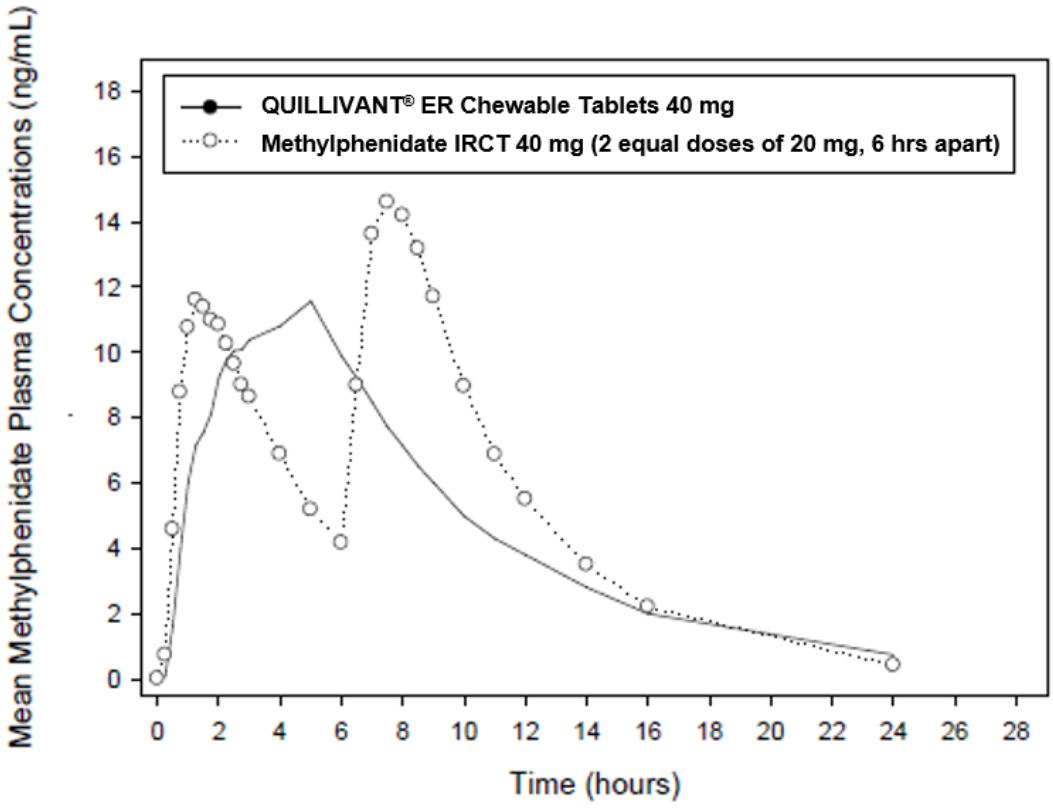
‡ data presented as median (range)

In a study in adult volunteers to investigate the effects of a high-fat meal on the bioavailability of QUILLIVANT® ER Oral Suspension at a dose of 60 mg, the presence of food reduced the time to peak concentration by approximately 1 hour (fed: 4 hours vs. fasted: 5 hours). Overall, a high-fat meal increased the average C_{max} of QUILLIVANT® ER Oral Suspension by about 28% and the AUC by about 19%. These changes are not considered clinically significant.

Following a single oral dose of 40 mg QUILLIVANT® ER Oral Suspension under fasting conditions, plasma methylphenidate reached maximal concentration (C_{max}) at a median time of 5 hours after dosing. Compared to an immediate-release formulation of methylphenidate chewable tablet (40 mg in 2 equal doses of 20 mg, 6 hours apart), methylphenidate mean peak concentration and exposure (AUC_{∞}) was about 20% and 11% lower, respectively, after single dose administration of 40 mg QUILLIVANT® ER Chewable Tablets (Figure 3).

Figure 3: **Mean Methylphenidate Plasma Concentration-Time Profiles After Administration of 40 QUILLIVANT® ER Chewable Tablets or Methylphenidate Immediate-Release Chewable Tablets (IRCT, 2 Equal Doses of 20 mg, 6 Hours Apart) Under Fasted Conditions in Healthy Volunteers**





A high-fat meal had no effect on the time to peak concentration, and increased C_{max} and systemic exposure (AUC_{∞}) of methylphenidate by about 20% and 4%, respectively, after a single dose

administration of 40 mg QUILLIVANT® ER Chewable Tablets.

Metabolism: In humans, methylphenidate is metabolized primarily via de-esterification to alpha-phenyl-piperidine acetic acid (PPAA). The metabolite has little or no pharmacologic activity.

Elimination: Plasma methylphenidate concentrations decline monophasically following oral administration. Following a single 60 mg oral dose of QUILLIVANT® ER Oral Suspension in 28 healthy adult subjects under fasting conditions, the mean plasma terminal elimination half-life of d-methylphenidate was 5.6 (± 0.8) hours. Following a single 40 mg dose of QUILLIVANT® ER Chewable Tablets the mean plasma terminal elimination half-life of methylphenidate was about 5.2 hours in healthy volunteers.

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose.

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of methylphenidate after QUILLIVANT® ER Oral Suspension administration were studied in pediatric patients with ADHD between 9 and 15 years of age. After a single oral dose of 60 mg QUILLIVANT® ER Oral Suspension, plasma concentrations of methylphenidate in children (9 to 12 years old; n=3) were approximately twice the concentrations observed in adults. There are no specific pediatric pharmacokinetic studies for QUILLIVANT ® ER. However, the pharmacokinetics of methylphenidate in pediatric patients 6 to 12 years old are not expected to be significantly different from adults following QUILLIVANT® ER Chewable Tablets administration.
- **Geriatrics:** Specific studies of QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets in geriatric patients have not been conducted.
- **Sex:** There is insufficient experience with the use of QUILLIVANT® ER Oral Suspension or QUILLIVANT® ER Chewable Tablets to detect gender variations in pharmacokinetics.
- **Ethnic Origin:** There is insufficient experience with the use of QUILLIVANT® ER Oral Suspension or QUILLIVANT® ER Chewable Tablets to detect ethnic variations in pharmacokinetics.
- **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:** There is no experience with the use of QUILLIVANT® ER Oral Suspension or QUILLIVANT® ER Chewable Tablets in patients with hepatic insufficiency.
- **Renal Insufficiency:** There is no experience with the use of QUILLIVANT® ER Oral Suspension or QUILLIVANT® ER Chewable Tablets in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPAA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of QUILLIVANT® ER Oral Suspension or QUILLIVANT® ER Chewable Tablets.

11 STORAGE, STABILITY AND DISPOSAL

Store QUILLIVANT® ER Oral Suspension and QUILLIVANT® ER Chewable Tablets at 15 to 30ºC. Dispense in original container.

Store reconstituted QUILLIVANT® ER Oral Suspension at 15 to 30ºC. QUILLIVANT® ER Oral Suspension is stable for up to 4 months after reconstitution.

Dispose of remaining, unused, or expired QUILLIVANT® ER Oral Suspension or QUILLIVANT® ER Chewable Tablets at the pharmacy. Do not discard with household trash.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

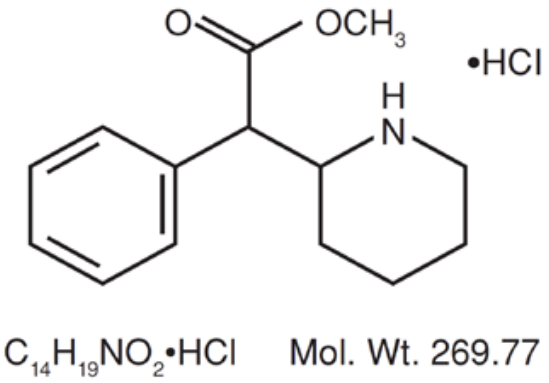
Drug Substance

Proper name: Methylphenidate hydrochloride

Chemical name: d,l(racemic) methyl α-phenyl-2-piperidineacetate hydrochloride

Molecular formula and molecular mass: $C_{14}H_{19}NO_2 \cdot HCl$, 269.77

Structural formula:



$C_{14}H_{19}NO_2 \cdot HCl$ Mol. Wt. 269.77

Physicochemical properties: Methylphenidate hydrochloride USP is a white, odourless crystalline powder

pH: methylphenidate hydrochloride solutions are acidic to litmus

pKa: 8.9

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

Melting Point: 224°C to 226°C

14 CLINICAL TRIALS

The efficacy of QUILLIVANT® ER Oral Suspension was evaluated in a laboratory classroom study conducted in 45 pediatric patients (ages 6 to 12 years) with ADHD. Patients in the trial met Diagnostic and Statistical Manual of Mental Diseases, 4th edition (DSM-IV®) criteria for ADHD. The study began with an open-label dose optimization period (4 to 6 weeks) with an initial QUILLIVANT® ER Oral Suspension dose of 20 mg once daily in the morning. The dose could be titrated weekly in increments of 10 or 20 mg until a therapeutic dose or the maximum dose of 60 mg/day was reached. At the end of the dose optimization period, approximately 6.8% of subjects were receiving 20 mg/day; 68.2%, 30 mg/day - 40 mg/day; 25%, 50 mg/day - 60 mg/day. Subjects then entered a 2-week randomized, double-blind, crossover treatment with the individually optimized dose of QUILLIVANT® ER Oral Suspension or placebo. At the end of each week, school teachers and raters evaluated the attention and behavior of the subjects in a laboratory classroom using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale. The SKAMP rating scale is a 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting and each item is rated on a 7-point impairment scale.

The efficacy of QUILLIVANT® ER Chewable Tablets was evaluated in a laboratory classroom study conducted in 90 pediatric subjects (ages 6 to 12 years) with ADHD. Patients in the trial met DSM-IV criteria for ADHD. The study began with a 6-week open-label dose optimization period with an initial QUILLIVANT® ER Chewable Tablets dose of 20 mg. Patients were instructed to chew each dose once daily in the morning. The dose could be titrated weekly in increments of 10 to 20 mg until a therapeutic dose or the maximum dose of 60 mg/day was reached. At the end of the dose optimization period, approximately 12.2% of subjects were receiving 20 mg/day; 43.3%, 30 mg/day - 40 mg/day; 44.5%, 50 mg/day - 60 mg/day.

14.1 Clinical Trials by Indication

Attention-Deficit Hyperactivity Disorder (ADHD)

QUILLIVANT®ER Oral Suspension

Table 6: Summary of patient demographics for the pivotal clinical trial of QUILLIVANT® ER Oral Suspension in ADHD (Study NWP06-ADD-100)*

Study Design	Dosage, Duration	Study subjects (n)	Mean age (Range)	Sex
Phase 3, dose-optimized, randomized, double-blind, placebo-controlled, multicenter, laboratory classroom study	**Open-Label Dose Optimization Period (6 weeks):** initial methylphenidate dose for all subjects was 20 mg once daily in the morning with weekly titrations in increments of 10 or 20 mg until an optimal dose or maximum dose (60 mg/day) was reached. **Double-blind treatment phase (2 weeks):** Subjects were treated with active methylphenidate for one week, followed by placebo for one week (Sequence A) or vice versa (Sequence B). Subjects were treated with the optimal dose that was established in the open- label, optimization phase.	44	8.8 years (6-12 years)	M-32 F-12

***Intent to treat population**

The SKAMP rating scale is a 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting and each item is rated on a 7-point impairment scale.

The primary efficacy endpoint was the SKAMP-Combined score at 4 hours post-dosing. The key secondary efficacy endpoints as determined by SKAMP-Combined scores at pre-dose and each post-dose (0.75, 2, 8, 10, and 12 hours) time point and each laboratory classroom day included onset and duration of clinical effect. The least-squares (LS) mean difference in SKAMP-Combined score at 4 hours post-dose was statistically significantly lower (i.e., more improved) with QUILLIVANT ER Oral Suspension compared to placebo. QUILLIVANT ER Oral Suspension was shown to have an onset of action within 0.75 hours ($p<0.0001$) and a duration of action of 12 hours ($p = 0.0016$) in children. Results from the two-week double-blind cross-over portion of the trial are summarized in Table 7.

Table 7: Primary Efficacy Result (ITT Population)

Scale Time-point	Statistic	Treatment		Treatment Difference (QUILLIVANT® ER Oral Suspension – Placebo) (N = 44)
		Placebo (N = 44)	QUILLIVANT® ER Oral Suspension (N = 44)	
SKAMP Combined Scale 4 Hours Post-Dose	N Mean (SD) Median Min, Max LS Mean (SE) 95% CI p-value Effect Size	39 19.3 (8.38) 19.0 4, 40 19.58 (1.14) (17.31, 21.86)	39 7.1 (5.64) 6.0 0, 30 7.12 (1.14) (4.85, 9.39)	39 -12.2 (7.19) -10.0 -25, 0 -12.49 (1.13) (-14.75, -10.17) <0.0001 2.519

Abbreviations: CI=confidence interval

QUILLIVANT® ER Chewable Tablets

Table 8: Summary of patient demographics for the pivotal clinical trial of QUILLIVANT® ER Chewable Tablets in ADHD (Study B7491005)*

Study Design	Dosage, Duration	Study subjects (n)	Mean age (Range)	Sex
Phase 3, dose-optimized, randomized, double-blind, placebo-controlled, multicenter, laboratory classroom study	**Open-Label Dose Optimization Period (6 weeks):** Methylphenidate hydrochloride ERCT 20-60 mg/day taken orally once daily in the morning before 10:00 am. Starting dose of 20 mg/day could be titrated up or down based on clinical judgment at weekly intervals in 10-20 mg/day increments to achieve a stable dose of 20-60 mg/day. **Double-blind treatment phase (1 week):** Subjects were randomized to receive methylphenidate hydrochloride ERCT (at the optimized dose) or placebo taken orally once daily in the morning before 10:00 am at the optimal dose established in	90	9.6 years (6-12 years)	M-53 F-32

Study Design	Dosage, Duration	Study subjects (n)	Mean age (Range)	Sex
	the Dose-Optimization Period.			

*Intent to treat population

Eighty-six (86) of the 90 enrolled subjects then entered a 1-week randomized, double-blind, parallel group treatment period with the individually optimized dose of QUILLIVANT® ER Chewable Tablets or placebo. The intent-to-treat (ITT) population consisted of 85 randomized subjects who received at least 1 dose of double-blind study drug and had at least 1 post-Baseline assessment of the primary efficacy variable. At the end of the double-blind treatment period, the laboratory classroom raters and teachers evaluated the attention and behavior of the subjects, throughout the day using the SKAMP rating scale.

The SKAMP-Combined score, measured at 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose during the laboratory classroom day at the end of the double-blind treatment period, was used to assess the primary and the key secondary efficacy parameters. The primary efficacy endpoint was the average of treatment effects across all the time points as specified above during the classroom day. The key secondary efficacy parameters were onset and duration of clinical effect.

The least-squares (LS) mean difference in the average of all post-dose SKAMP-Combined scores was statistically significantly lower (i.e., more improved) with QUILLIVANT ER Chewable Tablets compared to placebo. QUILLIVANT ER Chewable Tablets was shown to have an onset action within 2 hours ($p < 0.001$) and a duration of action of 8 hours ($p < 0.001$) in children. Results from the two-week double-blind cross-over portion of the trial are summarized in Table 9.

Table 9: Primary Efficacy Result (ITT Population)

Study Number	Treatment Group	Primary Efficacy Measure: Average of Treatment Effect Across All TimePoints Based on SKAMP-Combined Score		
		Mean Pre-dose Score on Classroom Day (SD)	LS Mean (SE) for the Classroom Day	Placebo-subtracted Difference[a] (95% CI)
Study 1	QUILLIVANT ER Chewable Tablets (N=42)	17.5 (11.6)	12.1 (1.4)	-7.0 (-10.9, -3.1)
	Placebo (N=43)	13.8 (10.0)	19.1 (1.4)	

N: number of patients; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence Interval.
[a]Least-squares Mean Difference (drug minus placebo).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity: In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 3.4 times the maximum recommended human dose (for a 30 kg child) on a mg/m^2 basis. Hepatoblastoma is a relatively rare

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

Methylphenidate did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 5 times the maximum recommended human dose on a mg/m^2 basis.

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

Reproductive and Developmental Toxicology: Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses of up to 160 mg/kg/day, approximately 8-fold the maximum recommended human dose on a mg/m^2 basis.

No teratogenic effects were seen in rats when given at a dose of 75 mg/kg/day, which are 37.5 and 8.2 times the maximum recommended human dose on a mg/kg and mg/m2 basis, respectively. In another study, however, methylphenidate was shown to be teratogenic in rabbits when given at a dose of 200 mg/kg/day, which are approximately 100 times and 40 times higher than the maximum recommended human dose on a mg/kg and mg/m2 basis, respectively.

Juvenile Toxicity: Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only.

In the study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal day 7) and continuing through sexual maturity (postnatal week 10). When these animals were tested as adults (postnatal weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 4.4 times the maximum human recommended dose MHRD] on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was observed in females exposed to the highest dose (approximately 9 times the MHRD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (approximately half the MHRD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

℄QUILLIVANT® ER Oral Suspension

Methylphenidate hydrochloride extended-release powder for oral suspension

Read this carefully before you start taking **QUILLIVANT® ER Oral Suspension** 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 **QUILLIVANT® ER Oral Suspension.**

Serious Warnings and Precautions

Drug Dependence

Like other stimulants, Quillivant ER Oral Suspension has the potential to be abused. This can lead to the child to becoming dependent on Quillivant ER Oral Suspension or feeling like they need to take more of it over time. Talk to the child's healthcare professional if you suspect that they are showing an interest in drugs or alcohol or have a tendency to abuse drugs and alcohol.

What is QUILLIVANT® ER Oral Suspension used for?

Quillivant ER Oral Suspension is used to treat Attention Deficit Hyperactivity Disorder (ADHD) in children 6-12 years of age.

Quillivant ER Oral Suspension is NOT recommended for use in children under 6 years of age.

The child's healthcare professional may include as part of their treatment with Quillivant ER Oral Suspension, other measures such as psychological counselling, educational and social measures, as part of their total treatment program.

How does QUILLIVANT® ER Oral Suspension work?

Quillivant ER Oral Suspension belongs to a group of medicines called central nervous system stimulants. It works by changing the levels of certain chemicals in the brain. This helps to increase attention and decrease impulsivity and hyperactivity in patients with ADHD.

What are the ingredients in QUILLIVANT® ER Oral Suspension?

Medicinal ingredients: Methylphenidate hydrochloride

Non-medicinal ingredients: Anhydrous citric acid, anhydrous trisodium citrate, banana flavour, corn starch, poloxamer, polyvinyl acetate, povidone, silicone dioxide, sodium benzoate, sodium polystyrene sulfonate, sucralose, sucrose, talc, triacetin, xanthan gum.

QUILLIVANT® ER Oral Suspension comes in the following forms:

Powder: 300 mg, 600 mg, 750 mg and 900 mg

Oral suspension (after reconstitution): 300 mg/60 mL, 600 mg/120 mL, 750 mg/150 mL and 900 mg/180 mL (5 mg/mL)

Do not use QUILLIVANT® ER Oral Suspension if the child:

- is allergic to methylphenidate hydrochloride, to any of the other ingredients in QUILLIVANT® ER Oral Suspension or to other central nervous system stimulants
- has an overactive thyroid gland (hyperthyroidism)
- has hardening of the arteries (advanced arteriosclerosis)
- has problems with their heart such as heart disease, had a heart attack, irregular heartbeat, chest pain, heart failure or was born with a heart problem
- has moderate to severe high blood pressure
- has glaucoma (an eye disease with increased pressure in the eye)
- is showing an interest in drugs
- is taking or has recently taken (within the past 14 days) any medications from a group of medicines called a monoamine oxidase inhibitor (MAOI).

To help avoid side effects and ensure proper use, talk to the child's healthcare professional before they take QUILLIVANT® ER Oral Suspension. Talk about any health conditions or problems they may have, including if the child:

- has heart problems, a heart defect, or there is a family history of sudden cardiac death
- has high blood pressure and is taking medicines to treat it
- does high-intensity exercise or activities
- is showing an interest in drinking alcohol
- has had seizures or abnormal EEGs (measure of brainwave activity)
- has movements or sounds they cannot control (tics) or they have Tourette's syndrome or there is a family history of these conditions
- has mental health problems or there is a family history of mental health problems, including:
    - anxiety
    - psychosis
    - mania
    - bipolar disorder
    - depression
    - aggression
    - suicide
- is taking other medicines for ADHD
- is pregnant, may be pregnant or is planning to become pregnant.
- is breastfeeding or planning to breast feed. QUILLIVANT® ER Oral Suspension can pass into your

breast milk. Consult with the child's healthcare professional to determine whether to stop breast-feeding or discontinue Quillivant ER Oral Suspension.

Other warnings you should know about:

Tasks requiring special attention: Quillivant ER Oral Suspension can affect the child's ability to perform certain tasks (e.g. riding a bike, driving a go-cart) and when using tools or machinery. They should not do these tasks until they know how they respond to Quillivant ER Oral Suspension.

Dependence and Tolerance: Like other stimulants, Quillivant ER Oral Suspension has the potential to be abused if not taken correctly which can lead to dependence and tolerance. If the child has a history of drug or alcohol abuse, discuss this with their healthcare professional. DO NOT change the dose or stop Quillivant ER Oral Suspension without first discussing this with their healthcare professional. If the child stops taking Quillivant ER Oral Suspension, they will need careful supervision because they 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. The child's healthcare professional will carefully watch their height and weight and may stop treatment if needed.

Heart Related Problems: The following heart related problems have been reported in people taking medicine to treat ADHD like QUILLIVANT® ER Oral Suspension:

- Sudden death in patients who have heart problems or heart defects
- Stroke and heart attack
- Increased blood pressure
- Increased heart rate

Tell the child's healthcare professional if they have any heart problems, heart defects, high blood pressure, or a family history of these problems. The child's healthcare professional will check:

- for heart problems before starting Quillivant ER Oral Suspension
- their blood pressure and heart rate regularly during treatment

Get medical help right away if the child has any signs of heart problems such as chest pain, difficulty breathing or fainting while taking QUILLIVANT® ER Oral Suspension.

Mental Health Problems: The following mental health problems have been reported in people taking medicine to treat ADHD like QUILLIVANT® ER Oral Suspension:

- New or worse thoughts or feelings of suicide (thinking about or feeling like killing yourself or harming others) and suicide attempt
- New or worse bipolar disorder (extreme mood swings, with periods of excitement, switching between periods of sadness)
- New or worse aggressive behavior or hostility, anxiety or feeling agitated
- 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 happen if the child has mental health conditions that you may or may not know about. These symptoms can happen at any time

during treatment but are more likely to occur when the child first starts taking QUILLIVANT® ER Oral Suspension, when their dose changes, or after they stop treatment.

Should this happen, consult the child's healthcare professional right away. Close observation by a healthcare professional is required.

Get medical help right away if the child has any mental health symptoms while taking QUILLIVANT® ER Oral Suspension.

Raynaud's Phenomenon: Stimulants used to treat ADHD, such as Quillivant ER Oral Suspension, are associated with Raynaud's Phenomenon. During treatment with Quillivant ER Oral Suspension, the child's healthcare professional may check for problems with the circulation in their fingers and toes, including numbness, feeling cold or pain.

Serotonin toxicity (also known as Serotonin Syndrome): Serotonin toxicity is a rare but potentially life-threatening condition. It can cause serious changes in how the child's brain, muscles and digestive system work. They may develop serotonin toxicity if they take Quillivant ER Oral Suspension with certain anti-depressants or migraine medications. Serotonin toxicity 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.

Testing and check-ups: The healthcare professional may do tests before the child starts treatment with Quillivant ER Oral Suspension and during their treatment. These tests may include:

- tests that check for problems in the heart or brain
- tests that check their blood pressure and heart rate
- blood tests to check complete blood count, platelet counts and liver enzymes

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

Serious Drug Interactions

The child MUST NOT take Quillivant ER Oral Suspension if they are:

- taking or has recently taken (within the past 14 days) a monoamine oxidase inhibitor (MAOI). It may cause serious side effects.
- taking clonidine (a medicine used to treat high blood pressure). It may cause serious side effects including sudden death.

The following may interact with QUILLIVANT® ER Oral Suspension:

- alcohol
- medicines used to prevent blood clots (commonly called "blood thinners"), such as warfarin
- medicines used to prevent seizures
- medicines used to treat depression or anxiety called 'selective serotonin reuptake inhibitors' (SSRIs) or serotonin and norepinephrine reuptake inhibitors' (SNRIs)
- medicines used to increase blood pressure

- medicines used to lower blood pressure
- medicines used to manage psychosis (antipsychotics)

How to take QUILLIVANT® ER Oral Suspension:

Take Quillivant ER Oral Suspension:

- Exactly as prescribed. Always follow the child's healthcare professional's instructions.
- From time to time, the child's healthcare professional may interrupt their treatment with Quillivant ER Oral Suspension to check their symptoms while they are not taking the medicine.

- **To avoid serious side effects:**
  - **DO NOT change the dose**
  - **The child MUST NOT stop taking Quillivant ER Oral Suspension without first consulting with a healthcare professional**

Usual dose:

Children (6-12 years of age): The child's health care professional will determine the best dose to treat their symptoms and may adjust the dose until it is right.

- Take the dose once a day in the morning with or without food. Use the dosing syringe provided in the carton to measure the dose.

Instructions For Use:

Step 1: Remove the bottle and oral dosing dispenser from the box (see Figure A). If the dosing syringe is missing or not provided, contact your pharmacist for a replacement.

Figure A

Step 2: Check and make sure that the bottle contains liquid medicine (see Figure B). If it is still in powder form, **do not use it**. Return it to your pharmacist.

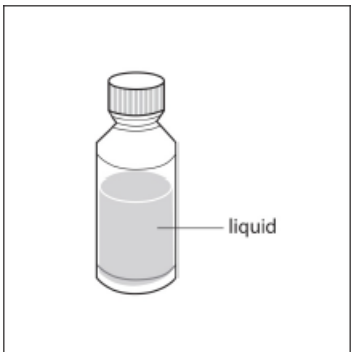


Figure B

Step 3: Shake the bottle well (vigorously up and down) for at lest 10 seconds before each use (see Figure C).

Figure C

Step 4: Uncap the bottle and check that the bottle adapter has been fully inserted into the bottle (see Figure D).

Figure D

If the bottle adapter (Figure E) has **not been inserted** by the pharmacist into the bottle, insert adapter into the bottle (see Figure F). The bottle adapter must be fully inserted (see Figure G) and should be even with the mouth of the bottle. It must remain in place to allow the child resistant cap to work the right way. After the bottle adapter has been fully inserted into the bottle, it should not be removed. If the bottle adapter has not been inserted and is missing from the box, contact your pharmacist.

Figure E

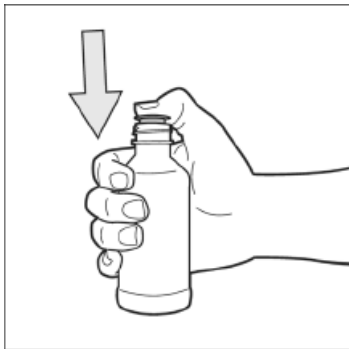


Figure F

Figure G

Step 5: Check the dose in millimeters (mL) as prescribed by the child's healthcare professional. Locate this number on the dosing syringe (see Figure H).

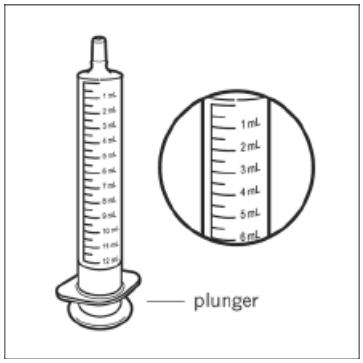


Figure H

Step 6: Insert tip of the dosing syringe into the upright bottle and push the plunger all the way down (see Figure I).

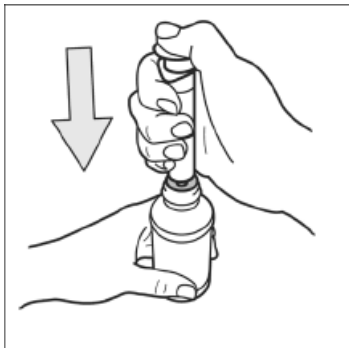


Figure I

Step 7: With the dosing syringe in place, turn the bottle upside down. Pull the plunger to the number of mL you need (the amount of liquid medicine in Step 5 – see Figure J). Measure the number of mL from the white end of the plunger (see Figure K).

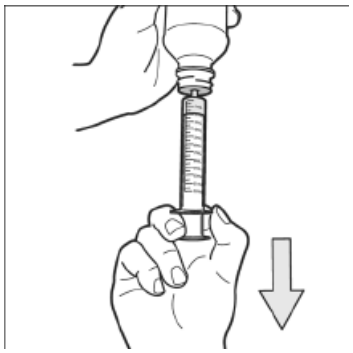


Figure J

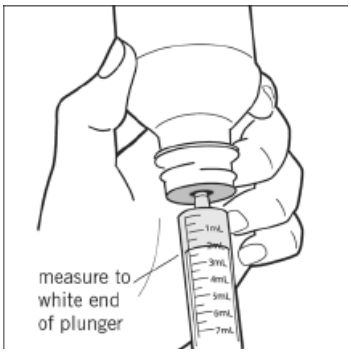


Figure K

Step 8: Remove the oral dosing dispenser from the bottle adapter.

Step 9: Slowly squirt QUILLIVANT® ER Oral Suspension directly into the child's mouth (see Figure L).

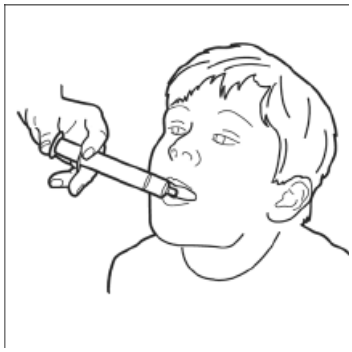


Figure L

Step 10: Cap the bottle tightly. Store the bottle upright at 15 to 30°C (see Figure M). Use the suspension within 4 months.

Figure M

Step 11: Clean the oral dosing dispenser after each use by placing in the dishwasher or by rinsing with tap water (see Figure N).

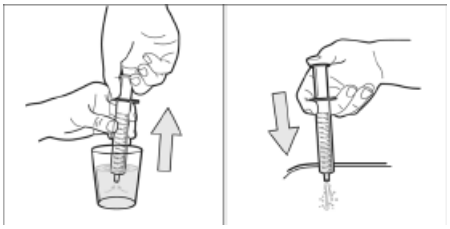


Figure N

Overdose:

If you think the child or a person you are caring for, has taken too much QUILLIVANT® ER Oral Suspension, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If a dose is missed, wait until the next day and take the usual dose at the usual time in the morning. DO NOT take the missed dose in the afternoon or double the dose the next morning to make up for the missed dose.

What are possible side effects from using QUILLIVANT® ER Oral Suspension?

These are not all the possible side effects the child may have when taking QUILLIVANT® ER Oral Suspension. If the child experiences any side effects not listed here, tell their healthcare professional.

Side effects include:

- headache
- trouble sleeping
- dizziness
- feeling tired
- feeling drowsy

- feeling anxious, nervous or jittery
- loss of appetite
- weight loss, weight gain
- sinus infection, common cold
- stomach pain
- indigestion
- nausea
- vomiting
- diarrhea
- dry mouth
- fast heart rate
- increased sweating
- difficulty opening the mouth (trismus)
- inability to control the bladder (incontinence)
- swelling of the breasts in boys or 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			
New or worsening mental health problems: paranoia, delusions, hallucinations (seeing, feeling or hearing things that are not there), mania (feeling unusually excited, over-active, or uninhibited)		✓	
COMMON			
Heart problems: fast or uneven heartbeat, chest pain, difficulty breathing, fainting			✓
Eye Problems: blurred vision, abnormal blinking or eyelid spasms		✓	
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.	✓		
Aggressive behaviour or hostility		✓	
UNKNOWN			
Suicidal Behaviour: thoughts or feelings about self-harm			✓
Raynaud's phenomenon episodes of reduced blood flow): discoloration of the fingers and toes, pain, sensations of cold and/or numbness		✓	
Seizures or Convulsions: incontrollable shaking, with or without loss of consciousness (fit)			✓
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)			✓
Serious Allergic Reaction: itching, skin rash, swelling of the mouth, face, lips, or tongue, trouble swallowing, trouble breathing			✓

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	
Priapism: long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
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		✓	
Edema: swollen hands, ankles or feet	✓		
Nosebleed	✓		

If the child has a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with their daily activities, tell their 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 QUILLIVANT® ER Oral Suspension (powder and reconstituted suspension) in the original container at room temperature (15°C - 30°C). Use the suspension within 4 months. Take any unused or expired Quillivant ER Oral Solution to the pharmacy for proper disposal. DO NOT throw it in household trash.

Keep out of reach and sight of children.

If you want more information about QUILLIVANT® ER Oral Suspension:

- 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 www.kyepharma.com, or by calling 1-888-822-7126.

This leaflet was prepared by KYE Pharmaceuticals Inc.

Last Revised September 11, 2023

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

℗ QUILLIVANT® ER Chewable Tablets

Methylphenidate hydrochloride extended-release chewable tablets

Read this carefully before you start taking **QUILLIVANT® ER Chewable Tablets** 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 **QUILLIVANT® ER Chewable Tablets**.

Serious Warnings and Precautions

Drug Dependence

Like other stimulants, Quillivant ER Chewable Tablets has the potential to be abused. This can lead to the child to becoming dependent on Quillivant ER Chewable Tablets or feeling like they need to take more of it over time. Talk to the child's healthcare professional if you suspect that they are showing an interest in drugs or alcohol or have a tendency to abuse drugs and alcohol.

What is QUILLIVANT® ER Chewable Tablets used for?

Quillivant ER Chewable Tablets are used to treat Attention Deficit Hyperactivity Disorder (ADHD) in children 6-12 years of age.

Quillivant ER Chewable Tablets are NOT recommended for use in children under 6 years of age.

The child's healthcare professional may include as part of their treatment with Quillivant ER Chewable Tablets, other measures such as psychological counselling, educational and social measures, as part of their total treatment program.

How does QUILLIVANT® ER Chewable Tablets work?

Quillivant ER Chewable Tablets belongs to a group of medicines called central nervous system stimulants. It works by changing the levels of certain chemicals in the brain. This helps to increase attention and decrease impulsivity and hyperactivity in patients with ADHD.

What are the ingredients in QUILLIVANT® ER Chewable Tablets?

Medicinal ingredients: Methylphenidate hydrochloride

Non-medicinal ingredients: Aspartame, cherry flavor, citric acid, crospovidone, D&C red (for 30 mg & 40 mg strengths), guar gum, magnesium stearate, maltodextrin, mannitol, microcrystalline cellulose, polyethylene glycol , polysorbate, polyvinyl acetate, polyvinyl alcohol, povidone, silicon dioxide, sodium lauryl sulfate, sodium polystyrene sulfonate, talc, triacetin, xanthan gum.

QUILLIVANT® ER Chewable Tablets comes in the following dosage forms:

Chewable tablets: 20 mg (scored), 30 mg (scored), and 40 mg

Do not use QUILLIVANT® ER Chewable Tablets if the child:

- is allergic to methylphenidate hydrochloride, to any of the other ingredients in QUILLIVANT® ER Chewable Tablets or to other central nervous system stimulants
- has an overactive thyroid gland (hyperthyroidism)
- has hardening of the arteries (advanced arteriosclerosis)
- has problems with their heart such as heart disease, had a heart attack, irregular heartbeat, chest pain, heart failure or was born with a heart problem
- has moderate to severe high blood pressure
- has glaucoma (an eye disease with increased pressure in the eye)
- is showing an interest in drugs
- is taking or has recently taken (within the past 14 days) any medications from a group of medicines called a monoamine oxidase inhibitor (MAOI).

To help avoid side effects and ensure proper use, talk to the child's healthcare professional before they take QUILLIVANT® ER Chewable Tablets. Talk about any health conditions or problems they may have, including if the child:

- has heart problems, a heart defect, or there is a family history of sudden cardiac death
- has high blood pressure and is taking medicines to treat it
- does high-intensity exercise or activities
- is showing an interest in drinking alcohol
- has had seizures or abnormal EEGs (measure of brainwave activity)
- has movements or sounds they cannot control (tics) or they have Tourette's syndrome or there is a family history of these conditions
- has mental health problems or there is a family history of mental health problems, including:
    - anxiety
    - psychosis
    - mania
    - bipolar disorder
    - depression
    - aggression
    - suicide
- is taking other medicines for ADHD
- has phenylketonuria (also called PKU). This is rare inherited disorder that causes phenylalanine to build up in the body. Quillivant ER Chewable Tablets contain aspartame, which is a source of phenylalanine.

- is pregnant, may be pregnant or is planning to become pregnant.
- is breastfeeding or planning to breast feed. QUILLIVANT® ER Chewable Tablets can pass into breast milk. Consult with the child's healthcare professional to determine whether to stop breast-feeding or discontinue Quillivant ER Chewable Tablets.

Other warnings you should know about:

Tasks requiring special attention: Quillivant ER Chewable Tablets can affect the child's ability to perform certain tasks (e.g. riding a bike, driving a go-cart) and when using tools or machinery. The child should not do these tasks until they know how they respond to Quillivant ER Chewable Tablets.

Dependence and Tolerance: Like other stimulants, Quillivant ER Chewable Tablets have the potential to be abused if not taken correctly which can lead to dependence and tolerance. If the child has a history of drug or alcohol abuse, discuss this with their healthcare professional. DO NOT change the dose or stop Quillivant ER Chewable Tablets without first discussing this with their healthcare professional. If the child stops taking Quillivant ER Chewable Tablets, they will need careful supervision because they 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. The child's healthcare professional will carefully watch their height and weight and may stop treatment if needed.

Heart Related Problems: The following heart related problems have been reported in people taking medicine to treat ADHD like Quillivant ER Chewable Tablets:

- Sudden death in patients who have heart problems or heart defects
- Stroke and heart attack
- Increased blood pressure
- Increased heart rate

Tell the child's healthcare professional if they have any heart problems, heart defects, high blood pressure, or a family history of these problems. The child's healthcare professional will check:

- for heart problems before starting Quillivant ER Chewable Tablets
- their blood pressure and heart rate regularly during treatment

Get medical help right away if the child has any signs of heart problems such as chest pain, difficulty breathing or fainting while taking QUILLIVANT® ER Chewable Tablets.

Mental Health Problems: The following mental health problems have been reported in people taking medicine to treat ADHD like QUILLIVANT® Chewable Tablets:

- New or worse thoughts or feelings of suicide (thinking about or feeling like killing themselves, or harming others) and suicide attempt
- New or worse bipolar disorder (extreme mood swings, with periods of excitement, switching between periods of sadness)
- New or worse aggressive behavior or hostility, anxiety or feeling agitated
- 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 happen if the child has mental health conditions that you may or may not know about. These symptoms can happen at any time

during treatment but are more likely to occur when the child first starts taking Quillivant ER Chewable Tablets, when their dose changes, or after they stop treatment.

Should this happen, consult the child's healthcare professional right away. Close observation by a healthcare professional is required.

Get medical help right away if the child has any mental health symptoms while taking QUILLIVANT® ER Chewable Tablets.

Raynaud's Phenomenon: Stimulants used to treat ADHD, such as Quillivant ER Chewable Tablets, are associated with Raynaud's Phenomenon. During treatment with Quillivant ER Chewable Tablets, the child's healthcare professional may check for problems with the circulation in their fingers and toes, including numbness, feeling cold or pain.

Serotonin toxicity (also known as Serotonin Syndrome): Serotonin toxicity is a rare but potentially life-threatening condition. It can cause serious changes in how the child's brain, muscles and digestive system work. The child may develop serotonin toxicity if they take Quillivant ER Chewable Tablets with certain anti-depressants or migraine medications. Serotonin toxicity 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.

Testing and check-ups: The healthcare professional may do tests before the child starts treatment with Quillivant ER Chewable Tablets and during their treatment. These tests may include:

- tests that check for problems in the heart or brain
- tests that check the child's blood pressure and heart rate
- blood tests to check complete blood count, platelet counts and liver enzymes

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

Serious Drug Interactions

The child MUST NOT take Quillivant ER Chewable Tablets if they are:

- taking or have recently taken (within the past 14 days) a monoamine oxidase inhibitor (MAOI). It may cause serious side effects.
- taking clonidine (a medicine used to treat high blood pressure). It may cause serious side effects including sudden death.

The following may interact with QUILLIVANT® ER Chewable Tablets:

- alcohol
- medicines used to prevent blood clots (commonly called "blood thinners"), such as warfarin
- medicines used to prevent seizures
- medicines used to treat depression or anxiety called 'selective serotonin reuptake inhibitors' (SSRIs) or serotonin and norepinephrine reuptake inhibitors' (SNRIs)

- medicines used to increase blood pressure
- medicines used to lower blood pressure
- medicines used to manage psychosis (antipsychotics)

How to take QUILLIVANT® ER Chewable Tablets:

Take Quillivant ER Chewable Tablets:

- Exactly as prescribed. Always follow the child's healthcare professional's instructions.
- The 20 mg and 30 mg chewable tablets are scored and can be broken in half, if needed, to get the right dose. The 40 mg chewable tablet are not scored and cannot be broken in half.
- From time to time, the child's healthcare professional may interrupt the child's treatment with Quillivant ER Chewable Tablets to check their symptoms while they are not taking the medicine.

- **To avoid serious side effects:**
  - **DO NOT change the dose**
  - **the child MUST NOT stop taking Quillivant ER Chewable Tablets without first consulting with a healthcare professional**

Usual dose:

Children (6-12 years of age): The child's health care professional will determine the best dose to treat their symptoms and may adjust the dose until it is right.

- Take the dose once a day in the morning with or without food.

Overdose:

If you think the child or a person you are caring for, has taken too much QUILLIVANT® ER Chewable Tablets, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If a dose is missed, wait until the next day and take the usual dose at the usual time in the morning. DO NOT take the missed dose in the or double the dose the next morning to make up for the missed dose.

What are possible side effects from QUILLIVANT® ER Chewable Tablets?

These are not all the possible side effects the child may have when taking QUILLIVANT® ER Chewable Tablets. If the child experiences any side effects not listed here, tell their healthcare professional.

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Eye Problems: blurred vision, abnormal blinking or eyelid spasms		✓	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in the ankles and legs, bluish colour to the lips and skin, racing pulse or fast or uneven heartbeat.	✓		
Aggressive behaviour or hostility		✓	
UNKNOWN			
Suicidal Behaviour: thoughts or feelings about self-harm			✓
Raynaud's phenomenon episodes of reduced blood flow): discoloration of the fingers and toes, pain, sensations of cold and/or numbness		✓	
Seizures or Convulsions: incontrollable shaking, with or without loss of consciousness (fit)			✓
Tourette's Syndrome: motor tics (hard-to-control, repeated twitching of any part of the child's body) and verbal tics (hard-to-control repeating of sounds or words)			✓
Serious Allergic Reaction: itching, skin rash, swelling of the mouth, face, lips, or tongue, trouble			✓

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
swallowing, trouble breathing			
Priapism: long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
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		✓	
Edema: swollen hands, ankles or feet	✓		
Nosebleed	✓		

If the child has a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with their daily activities, tell their healthcare professional.

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This leaflet was prepared by KYE Pharmaceuticals Inc.

Last Revised September 20, 2023