PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

FOQUEST®

methylphenidate hydrochloride

25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg and 100 mg Controlled Release Capsules, Oral

Professed Standard

Central Nervous System Stimulant

Elvium Life Sciences

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Toronto, Ontario

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Date of Initial Authorization:
December 5, 2017

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Submission Control Number: 257460

RECENT MAJOR LABEL CHANGES

Not applicable

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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

FOQUEST® (methylphenidate hydrochloride controlled release capsules) is indicated for:

- The treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients ≥6 years of age.

Long-Term Use
The effectiveness of FOQUEST has not been evaluated for more than four weeks in placebo-controlled clinical trials (see 14 CLINICAL TRIALS). If electing to use FOQUEST for extended periods, the long-term usefulness of the drug for the individual patient should be periodically re-evaluated (see 4 DOSAGE AND ADMINISTRATION).

Need for Comprehensive Treatment Program
FOQUEST is indicated as an integral part of a total treatment program for ADHD that may include other measures (i.e., psychological, educational and/or social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Drug treatment is not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential in patients with this diagnosis and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment will depend upon the health professional's assessment of the chronicity and severity of the patient's symptoms and on the level of functional impairment.

1.1 Pediatrics

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

Pediatrics (6 – 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of FOQUEST in pediatric patients (6 years of age and older) has been established. Therefore, Health Canada has authorized an indication for pediatric use (see 4.2 Recommended Dose and Dosage Adjustment)**.**

1.2 Geriatrics

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

2 CONTRAINDICATIONS

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

Additionally, FOQUEST is 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 9.4 Drug-Drug Interactions)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
• Drug Dependence – Like other stimulants, FOQUEST has the potential to be abused, leading to dependence and tolerance (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

4.2 Recommended Dose and Dosage Adjustment

- **General**

  FOQUEST controlled release capsules are for oral administration once daily in the morning, with or without food.

  The effect of FOQUEST might last into the evening, take as soon as possible in the morning to avoid any potential effect on sleep.

- **Patients New to Methylphenidate**

  The usual initial dose should be 25 mg once-daily in the morning. If a dose increase is warranted in the judgment of the physician, the daily dose may be adjusted to the lowest effective dose in intervals of no less than 5 days. The maximum daily dose for children and adolescents (6 to <18 years old) is 70mg. The maximum daily dose for adults (≥18 years old) is 100 mg.

- **Patients Currently Taking Methylphenidate**

  The recommended starting dose of FOQUEST is the next lower strength based on the total methylphenidate daily dose. If a dose increase is warranted in the judgment of the physician, the daily dose may be adjusted to the lowest effective dose in intervals of no less than 5 days. The maximum daily dose for children and adolescents (6 to <18 years old) is 70 mg. The maximum daily dose for adults (≥18 years old) is 100 mg.

  Do not substitute for immediate release methylphenidate tablets or other controlled release methylphenidate products on a milligram for milligram basis because of differing pharmacokinetic profiles.

- **Long-term Use**

  There is no evidence available from controlled trials to indicate how long a patient with ADHD should be treated. Pharmacological treatment of ADHD may be needed for extended periods. The safety and efficacy of FOQUEST in children with ADHD was studied in an 8-week controlled, parallel-group, double-blind, laboratory classroom trial. The safety and efficacy of FOQUEST in adolescents and adults with ADHD were studied in two 4 week, placebo-controlled randomized trials. The safety of FOQUEST was further evaluated in a 6-month open-label trial (see 14 CLINICAL TRIALS).

  The clinician who elects to use FOQUEST for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

- **Dose Reduction and Discontinuation**

  If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or if necessary, discontinue the drug. If little or no improvement is observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

4.4 Administration

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

For patients unable to swallow the capsule, the capsule may be opened and the entire contents sprinkled onto a tablespoon of applesauce, ice cream or yogurt. Do not sprinkle in liquids. The entire mixture should be consumed **immediately or within 10 minutes** without chewing and should be discarded if not consumed. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and patients should not take anything less than one capsule per day. Ingestion should be followed by rinsing the mouth with water to ensure that the entire contents are swallowed.

4.5 Missed Dose

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

5 OVERDOSAGE

Signs and symptoms of acute overdose, resulting principally from overstimulation of the 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 FOQUEST capsules should be considered when treating patients with overdose.

Alcohol may induce the production of ethylphenidate. The amount of ethylphenidate production is proportional to the blood alcohol concentration (see 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 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Controlled Release Capsules 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg and 100 mg	ammonio methacrylate copolymer dispersion (type B), anionic copolymer (consisting of methyl acrylate, methyl methacrylate and methacrylic acid), glyceryl monostearate, hypromellose, polyethylene glycol, polysorbate, silicon dioxide, sodium hydroxide, sodium lauryl sulfate, sorbic acid, sugar spheres, triethyl citrate

*See Table 2 for non-medicinal ingredients associated with capsule shell colours

FOQUEST is a capsule formulation that uses MLR® bead technology. Each bead consists of multiple concentric layers of drug and drug release-controlling excipients with 20% of the total methylphenidate dose contained in an immediate release layer and 80% contained in delayed controlled release layers for once daily oral administration.

FOQUEST is available in the following strengths (see Table 2):

Table 2: FOQUEST Capsule Colour by Strengths

Strength (mg)	*Capsule Colour*	*Non-medicinal Ingredients in Capsule Shell Colours*
25 mg	Blue	FD&C Blue No. 1
35 mg	Orange	FD&C Yellow No. 6, Titanium Dioxide
45 mg	Yellow	FD&C Yellow No. 5, Titanium Dioxide
55 mg	Light green	FD&C Blue No. 1, Titanium Dioxide, Yellow Iron Oxide
70 mg	Iron gray	Black Iron Oxide, Titanium Dioxide
85 mg	White	Titanium Dioxide
100 mg	Cream	Red Iron Oxide, Titanium Dioxide, Yellow Iron Oxide

Each capsule is imprinted with "MLR-02" and a number corresponding to the strength, in milligrams (mg), in black ink. All dosage strengths are supplied in bottles containing 60 capsules.

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 FOQUEST 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 stimulants; or c) have a family history of sudden/cardiac death. Prior to the initiation of treatment, a personal and family history (including assessment for a family history sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease. In patients with relevant risk factors and based on the clinician's judgement, further cardiovascular evaluation may be considered (e.g., electrocardiogram [ECG] 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.
- Plasma Concentration of FOQUEST: Pharmacokinetic studies show that after dosing FOQUEST 100 mg, there is approximately 9-20% residual methylphenidate in the blood at 24 hours.
- Fatigue: FOQUEST should not be used for the prevention or treatment of normal fatigue states.
- Patients should be advised not to take alcohol with FOQUEST (see 9.3 Drug-Behavioural Interactions).

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, FOQUEST 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 condition of the cardiovascular or cerebrovascular system, taking into account risk predictors for these conditions. Patients should be screened for pre-existing or underlying cardiovascular or cerebrovascular conditions before initiation of treatment with stimulants and monitored for new conditions of the heart or brain during the course of treatment.

- **Hypertension and Other Cardiovascular Conditions:**

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

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

  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 a 4-week double-blind, placebo-controlled study of FOQUEST up to 100 mg/day in adults, changes in mean systolic blood pressure (range of mean increase: 0.29 to 1.60 mmHg), diastolic blood pressure (range of mean increase: 0.123 to 1.75 mmHg) and heart rate (range of mean increase: 1.04 to 4.98 bpm) were observed. 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 2 CONTRAINDICATIONS and 9 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

FOQUEST should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

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

Careful supervision is required during 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 FOQUEST 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. 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 FOQUEST, 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 FOQUEST 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 FOQUEST and other serotonergic agents should be considered and appropriate treatment instituted.

Ophthalmologic

- **Visual Disturbance:**

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

Psychiatric

- **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:**

  FOQUEST 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/m2 basis, respectively.

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

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 FOQUEST therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman.

7.1.3 Pediatrics

Pediatrics (6 – 18 years of age): The safety of FOQUEST in adolescent patients has been studied in a 6-month open-label trial. Long-term effects of FOQUEST have not been well established beyond 6 months in adolescents (12 to 17 years old) and 7 weeks in children (6 to 11 years old).

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

7.1.4 Geriatrics

FOQUEST has not been studied in the geriatric population (>65 years of age); therefore, Health Canada has not authorized an indication for geriatric use (see 1.2 Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Commonly reported (≥2% of the methylphenidate group and twice the rate of the placebo group) adverse reactions from placebo-controlled trials of FOQUEST include: appetite decreased, weight decreased, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, dizziness, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, fatigue and pyrexia.

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 FOQUEST (methylphenidate hydrochloride controlled release capsules) included exposures in 582 adults, 293 adolescents and 156 children with a total of 1031 ADHD patients (≥6 years of age) in two 4-week parallel group, double-blind clinical trials, a controlled, parallel-group, double-blind, laboratory classroom trial in adults and a controlled, parallel-group, double-blind, laboratory classroom trial in children. One hundred and eighty-four adults and 178 adolescents who participated in the double-blind studies were further evaluated in a 6-month open-label trial.

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 FOQUEST treatment mainly reflect side effects commonly associated with methylphenidate use. Very common AEs reported by patients treated with FOQUEST were: headache, insomnia, decreased appetite and abdominal pain. Most of the events were mild or moderate in severity.

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

- **Adults (≥18 years of age)**

  In a placebo-controlled, double-blind, trial in adults (≥18 years of age), during the double-blind treatment period, 2.7% (8/297) of FOQUEST-treated patients discontinued treatment due to AEs compared to 2.6% (2/78) who received placebo. AEs that led to discontinuation included: anxiety 0.7% (2/297); insomnia 0.7% (2/297); lip swelling 0.3% (1/297); affect lability 0.3% (1/297); emotional disorder 0.3% (1/297); and irritability 0.3% (1/297). One SAE of uterine cancer occurred.

In a second placebo-controlled, double-blind, trial in adults (≥18 years of age), during the open-label treatment period, 3.5% (10/285) of FOQUEST-treated participants discontinued treatment due to AEs; one subject (0.4%) with decreased appetite, anxiety and insomnia, one subject (0.4%) with headache and flat affect, and one subject each with ST segment depressed (0.4%), jitteriness (0.4%), heart palpitations (0.4%), irritability (0.4%), anxiety (0.4%), nausea (0.4%), headache (0.4%). One SAE of acute paranoia (0.4%) occurred.

In a six-month open-label, safety trial 4.9% (9/184) of FOQUEST-treated adult patients discontinued treatment due to AEs. AEs leading to discontinuation included: insomnia 1.1% (2/184); weight decreased 0.5% (1/184); balance disorder 0.5% (1/184), viith nerve paralysis 0.5% (1/184); anxiety 0.5% (1/184); depression 0.5% (1/184); irritability 0.5% (1/184); and nervousness 0.5% (1/184). SAEs included tendon rupture (n = 1), breast cancer (n = 1), dizziness (n = 1) and viith nerve paralysis (n = 1).

TEAEs reported in controlled trials in adult patients with ADHD treated with FOQUEST with an incidence greater or equal to 1% are presented in the tables below, divided by study.

Table 3: Treatment Emergent Adverse Events Reported by ≥1% of Adults (≥18 years of age) with ADHD*

	FOQUEST n = 297 (%)	**Placebo n = 78 (%)**
Cardiac Disorders		
Palpitations	4 (1.3)	1 (1.3)
Tachycardia	4 (1.3)	0
Eye Disorders		
Vision blurred	4 (1.3)	0
Gastrointestinal disorders		
Abdominal pain	4 (1.3)	0
Abdominal pain upper	6 (2.0)	0
Diarrhea	12 (4.0)	1 (1.3)
Dry mouth	27 (9.1)	3 (3.8)
Dyspepsia	5 (1.7)	2 (2.6)
Nausea	18 (6.1)	2 (2.6)
Vomiting	4 (1.3)	1 (1.3)
General disorders and administration site conditions		
Fatigue	13 (4.4)	4 (5.1)
Feeling jittery	12 (4.0)	1 (1.3)
Thirst	4 (1.3)	0

	FOQUEST n = 297 (%)	Placebo n = 78 (%)
Infections and infestations		
Sinusitis	3 (1.0)	1 (1.3)
Upper respiratory tract infection	7 (2.4)	1 (1.3)
Urinary tract infection	3 (1.0)	0
Investigations		
Blood pressure increased	3 (1.0)	0
Weight decreased	11 (3.7)	1 (1.3)
Metabolism and nutrition disorders		
Decreased appetite	33 (11.1)	2 (2.6)
Musculoskeletal and connective tissue disorders		
Back pain	3 (1.0)	0
Muscle tightness	3 (1.0)	0
Nervous system disorders		
Dizziness	5 (1.7)	0
Headache	52 (17.5)	9 (11.5)
Paraesthesia	3 (1.0)	0
Somnolence	6 (2.0)	3 (3.8)
Tension headache	4 (1.3)	0
Psychiatric disorders		
Agitation	5 (1.7)	0
Anxiety	6 (2.0)	1 (1.3)
Bruxism	5 (1.7)	0
Emotional disorder	4 (1.3)	0
Insomnia[a]	67 (22.6)	4 (5.1)
Irritability	16 (5.4)	4 (5.1)
Restlessness	5 (1.7)	0
Sleep disorder	3 (1.0)	0

	FOQUEST n = 297 (%)	Placebo n = 78 (%)
Reproductive system and breast disorders		
Dysmenorrhea	3 (1.0)	0
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	3 (1.0)	0
Skin and subcutaneous tissue disorders		
Hyperhidrosis	4 (1.3)	0

[a] Insomnia includes TEAEs reported for "insomnia", "initial insomnia", and "middle insomnia"

*(Study Duration: 4 weeks, Doses: 25, 45, 70 and 100 mg/day)

Table 4: Treatment Emergent Adverse Events Reported by ≥1% of Adults (≥18 years of age) with ADHD in a Laboratory Classroom Study with up to 7 Weeks Open Label Titration Phase followed by a 1 Week Double Blind Treatment Phase*

Preferred Term	Open Label Phase (up to 7 weeks)	Double Blind Phase (1 week)	
	FOQUEST n=285 (%)	FOQUEST n=121 (%)	PLACEBO n=118 (%)
Psychiatric Disorders			
Insomnia	46 (16.1%)	2 (1.7%)	2 (1.7%)
Irritability	27 (9.5%)	2 (1.7%)	0
Initial insomnia	9 (3.2%)		
Affect lability	8 (2.8%)	0	1 (0.8%)
Anxiety	17 (6.0%)	1 (0.8%)	0
Libido decreased	4 (1.4%)		
Restlessness	5 (1.8%)		
Abnormal dreams	3 (1.1%)		
Constricted affect	3 (1.1%)		
Agitation	3 (1.1%)		
Apathy	4 (1.4%)		

Gastrointestinal Disorders			
Dry Mouth	25 (8.8%)		
Nausea	20 (7.0%)	2 (1.7%)	0
Abdominal pain upper	12 (4.2%)		
Diarrhoea	10 (3.5%)	1 (0.8%)	0
Gastroesophageal reflux disorder	5 (1.8%)		
Vomiting	9 (3.2%)	0	1 (0.8%)
Constipation	4 (1.4%)		
Dyspepsia	5 (1.8%)		
Flatulence	3 (1.1%)	1 (0.8%)	0
Toothache	3 (1.1%)	0	1 (0.8%)
Gastritis	3 (1.1%)		
Nervous System Disorders			
Headache	61 (21.4%)	5 (4.1%)	3 (2.5%)
Dizziness	5 (1.8%)	1 (0.8%)	0
Delayed sleep phase	4 (1.4%)	1 (0.8%)	0
Paraesthesia	3 (1.1%)		
Somnolence	3 (1.1%)		
Lethargy	6 (2.1%)		
Sedation	3 (1.1%)		

Metabolism and Nutrition Disorders			
Decreased appetite	61 (21.4%)	1 (0.8%)	0
Increased appetite	5 (1.8%)		
Infections and infestations			
Upper respiratory tract infection	26 (9.1%)	2 (1.7%)	3 (2.5%)
Nasopharyngitis	13 (4.6%)		
Pharyngitis	3 (1.1%)		
Gastroenteritis	3 (1.1%)		
Influenza	4 (1.4%)		
Sinusitis	6 (2.1%)		
General disorders and administration site conditions			
Feeling jittery	12 (4.2%)		
Fatigue	15 (5.3%)	4 (3.3%)	1 (0.8%)
Pyrexia	3 (1.1%)		
Chest discomfort	3 (1.1%)		
Investigations			
Blood pressure diastolic increased	6 (2.1%)		
Blood pressure increased	5 (1.8%)	1 (0.8%)	0
Heart rate increased	5 (1.8%)	0	1 (0.8%)
Weight decreased	4 (1.4%)		
Musculoskeletal and connective tissue disorders			
Myalgia	8 (2.8%)	1 (0.8%)	1 (0.8%)
Muscle spasms	4 (1.4%)		
Back pain	4 (1.4%)	0	1 (0.8%)

Skin and subcutaneous tissue disorders			
Dermatitis contact	4 (1.4%)		
Hyperhidrosis	3 (1.1%)		
Respiratory, thoracic and mediastinal disorders			
Cough	4 (1.4%)	0	1 (0.8%)
Nasal congestion	5 (1.8%)		
Oropharyngeal pain	3 (1.1%)		
Sinus congestion	3 (1.1%)		
Eye disorders			
Lacrimation increased	4 (1.4%)		
Cardiac disorders			
Tachycardia	6 (2.1%)		
Palpitations	3 (1.1%)		
Reproductive system and breast disorders			
Dysmenorrhea		2 (1.7%)	0

*Study Duration: up to 8 weeks. Open-Label Phase: All participants started at 25 mg/day. Doses were titrated each week to the next highest dose according to tolerability: 25, 35, 45, 55, 70, 85 and 100 mg/day. Participants may have returned to a lower dose if necessary. When optimal dose was reached participants entered Double Blind, placebo-controlled Phase (half of the participants were randomized to receive placebo while the other half remained on their optimised dose).

Adverse Events Occurring in a 6 month Safety Trial in Adults:

A 6-month open-label clinical trial was performed to evaluate the long-term safety of FOQUEST in adults. The 184 adults who completed the double-blind, placebo-controlled phase III trials (063-010) also participated in a 6-month open-label trial. TEAEs reported in this trial are provided in Table 5.

Overall, treatment with FOQUEST was well tolerated and the safety profile was consistent with other methylphenidate products. The majority of TEAEs (98%) were mild to moderate in intensity, with 8 adult (4.3%) participants who withdrew early due to an AE. In addition, there were no clinically significant laboratory, vital signs, ECG or sleep quality (as assessed by the Pittsburgh Sleep Quality Index [PSQI]) findings. The AE profile seen in the extension trial was similar to that observed in shorter term trials.

Table 5: Treatment-Emergent Adverse Events Reported by ≥5% of Adults (≥18 years of age) with ADHD treated with FOQUEST in a 6-month Open-Label Clinical Trial

	FOQUEST n = 363 (%)
	Adult (n=185)
Gastrointestinal disorders	
Dry Mouth	12 (6.5%)
Nausea	13 (7.0%)
General disorders and administration site conditions	
Feeling Jittery	10 (5.4%)
Infections and infestations	
Sinusitis	10 (5.4%)
Upper respiratory tract infection	13 (7.0%)
Metabolism and nutrition disorders	
Decreased appetite	15 (8.1%)
Nervous system disorders	
Headache	20 (10.8%)
Psychiatric disorders	
Anxiety	13 (7.0%)
Insomnia[a]	54 (30.3%)
Irritability	12 (6.5%)

[a] Insomnia includes TEAEs reported for "insomnia", "initial insomnia", and "middle insomnia"

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)**

  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, 1.3% (2/156) of FOQUEST-treated patients discontinued treatment due to AEs; one subject (0.6%) with affect lability and dermatillomania and one subject (0.6%) with ECG PR prolongation. There were no SAEs reported.

- **Adolescents (12 to 17 years of age)**

  In a placebo-controlled, double-blind trial in adolescents, 3.4% (10/293) of FOQUEST-treated patients discontinued treatment due to AEs. The AEs that led to discontinuation were irritability (three of 293 subjects; 1.0%) and anxiety, delirium, depressed mood, dysphoria, suicidal ideation, dizziness, and headache (each one of 293 subjects, 0.3%). There were no SAEs reported. In a six-month open-label, safety trial, 5.0% (9/179) of subjects discontinued due to AEs, one subject each (0.6%) with asthma exacerbation, depressed mood, flat affect, generalized anxiety disorder, insomnia, decreased appetite, headache, urticaria chronic, and severe aggressive behaviour. Two subjects experienced SAEs including asthma exacerbation and severe aggressive behaviour.

TEAEs reported in controlled trials in children and adolescent patients with ADHD treated with FOQUEST with an incidence greater or equal to 1% are presented in the tables below, divided by study.

Table 6: 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 Phase followed by a 1 Week Double Blind Treatment Phase*

Preferred Term	Open Label Phase (up to 6 weeks)	Double Blind Phase (1 week)	
	FOQUEST n = 156 (%)	FOQUEST n = 83 (%)	Placebo n = 73 (%)
Cardiac Disorders			
Sinus tachycardia	6 (3.8)	1 (1.3)	2 (2.7)
Tachycardia		1 (1.3)	0 (0)
Ear and labyrinth disorders			
Ear canal erythema		0 (0)	1 (1.4)
Gastrointestinal disorders			
Abdominal pain upper	26 (16.7)	1 (1.3)	0 (0)
Diarrhoea	7 (4.5)		
Dry mouth	3 (1.9)		
Nausea	9 (5.8)	1 (1.3)	0 (0)
Toothache		0 (0)	1 (1.4)
Vomiting	15 (9.6)	2 (2.7)	0 (0)
General disorders and administration site conditions			
Fatigue	6 (3.8)		
Pyrexia	3 (1.9)		
Infections and infestations			
Bronchitis		0 (0)	1 (1.4)

Preferred Term	Open Label Phase (up to 6 weeks)	Double Blind Phase (1 week)	
	FOQUEST n = 156 (%)	FOQUEST n = 83 (%)	Placebo n = 73 (%)
Gastroenteritis	2 (1.3)		
Gastroenteritis viral	3 (1.9)		
Impetigo		0 (0)	1 (1.4)
Upper respiratory tract infection	9 (5.8)	2 (2.7)	0 (0)
Injury, poisoning and procedural complications			
Arthropod bite		1 (1.3)	0 (0)
Contusion	2 (1.3)		
Eye contusion		1 (1.3)	0 (0)
Laceration	3 (1.9)		
Muscle strain	2 (1.3)		
Investigations			
Heart rate increased	9 (5.8)	3 (4.0)	1 (1.4)
Blood pressure diastolic increased	3 (1.9)	1 (1.3)	0 (0)
Blood pressure systolic increased	4 (2.6)		
Weight decreased	18 (11.5)	1 (1.3)	0 (0)
Metabolism and nutrition disorders			
Decreased appetite	55 (35.3)	1 (1.3)	0 (0)
Musculoskeletal and connective tissue disorders			
Myalgia		1 (1.3)	0 (0)
Nervous system disorders			
Dizziness	4 (2.6)		
Facial spasm	2 (1.3)		
Headache	17 (10.9)	2 (2.7)	0 (0)
Hypersomnia		0 (0)	1 (1.4)
Psychiatric disorders			

Preferred Term	Open Label Phase (up to 6 weeks)	Double Blind Phase (1 week)	
	FOQUEST n = 156 (%)	FOQUEST n = 83 (%)	Placebo n = 73 (%)
Affect lability	22 (14.1)		
Anxiety	2 (1.3)		
Initial insomnia	3 (1.9)		
Insomnia	16 (10.3)		
Irritability	16 (10.3)	1 (1.3)	0 (0)
Nightmare	3 (1.9)		
Reproductive system and breast disorders			
Dysmenorrhea		1 (1.3)	0 (0)
Respiratory, thoracic and mediastinal disorder			
Cough	2 (1.3)		
Epistaxis		0 (0)	1 (1.4)
Skin and subcutaneous tissue disorders			
Rash	2 (1.3)		

*Study Duration: up to 7 weeks., Open-Label Phase: All participants started at 25 mg/day. Doses were titrated each week to the next highest dose according to tolerability: 25, 35, 45, 55, 70 and 85 mg/day. Participants may have returned to a lower dose if necessary. When optimal dose was reached participants entered Double Blind, placebo-controlled Phase (half of the participants were randomized to receive placebo while the other half remained on their optimised dose).

Table 7: Treatment-Emergent Adverse Events Reported by ≥1% of Adolescents (12 to 17 years of age) with ADHD*

	FOQUEST n = 293 (%)	Placebo n = 74 (%)
Cardiac Disorders		
Tachycardia	4 (1.4)	1 (1.4)
Gastrointestinal disorders		
Abdominal discomfort	(2.0)	1 (1.4)
Abdominal pain	3 (1.0)	1 (1.4)
Abdominal pain upper	17 (5.8)	2 (2.7)
Dry mouth	8 (2.7)	1 (1.4)

	FOQUEST n = 293 (%)	Placebo n = 74 (%)
Nausea	17 (5.8)	3 (4.1)
Vomiting	8 (2.7)	0 (0)
General disorders and administration site conditions		
Fatigue	10 (3.4)	4 (5.4)
Infections and infestations		
Nasopharyngitis	7 (2.4)	1 (1.4)
Otitis externa	3 (1.0)	1 (1.4)
Upper respiratory tract infection	11 (3.8)	3 (4.1)
Injury, poisoning and procedural complications		
Confusion	5 (1.7)	1 (1.4)
Laceration	3 (1.0)	0 (0)
Ligament Sprain	4 (1.4)	1 (1.4)
Investigations		
Blood pressure decreased	3 (1.0)	0 (0)
Blood pressure increased	4 (1.4)	1 (1.4)
Heart rate increased	4 (1.4)	0 (0)
Weight decreased	22 (7.5)	0 (0)
Weight increased	10 (3.4)	2 (2.7)
Metabolism and nutrition disorders		
Decreased appetite	59 (20.1)	0 (0)
Musculoskeletal and connective tissue disorders		
Pain in extremity	3 (1.0)	0 (0)
Nervous system disorders		
Dizziness	11 (3.8)	1 (1.4)
Headache	44 (15.0)	7 (9.5)
Lethargy	3 (1.0)	0 (0)
Sedation	3 (1.0)	1 (1.4)

	FOQUEST n = 293 (%)	Placebo n = 74 (%)
Somnolence	3 (1.0)	2 (2.7)
Psychiatric disorders		
Affect lability	3 (1.0)	1 (1.4)
Aggression	3 (1.0)	2 (2.7)
Anxiety	3 (1.0)	0 (0)
Insomnia[a]	24 (11.6)	2 (2.8)
Irritability	24 (8.2)	7 (9.5)
Sleep disorder	8 (2.7)	2 (2.7)
Reproductive system and breast disorders		
Dysmenorrhea	3 (1.0)	2 (2.7)
Respiratory, thoracic and mediastinal disorder		
Cough	4 (1.4)	0 (0)
Oropharyngeal pain	3 (1.0)	0 (0)

[a] Insomnia includes TEAEs reported for “insomnia”, “initial insomnia”, and “middle insomnia”

*(Study Duration: 4 weeks, Doses: 25, 45, 70 and 85 mg/day)

Adverse Events Occurring in a 6 month Safety Trial in Adolescents (12 to 17 years old):

A 6-month open-label clinical trial was performed to evaluate the long-term safety of FOQUEST in adolescents. The 178 adolescents who completed the double-blind, placebo-controlled phase III trials (063-009) also participated in a 6-month open-label trial. TEAEs reported in this trial are provided in Table 8.

Overall, treatment with FOQUEST was well tolerated and the safety profile was consistent with other methylphenidate products. The majority of TEAEs (98%) were mild to moderate in intensity, with 9 adolescent (5.0%) participants who withdrew early due to an AE. In addition, there were no clinically significant laboratory, vital signs, ECG or sleep quality (as assessed by the Pittsburgh Sleep Quality Index [PSQI]) findings. The AE profile seen in the extension trial was similar to that observed in shorter term trials.

Table 8: Treatment-Emergent Adverse Events Reported by ≥5% of Adolescents (12 to 17 years of age) with ADHD treated with FOQUEST in a 6-month Open-Label Clinical Trial

	FOQUEST n = 363 (%)
	Adolescent (n=178)
Gastrointestinal disorders	
Nausea	9 (5.1%)
Infections and infestations	
Nasopharyngitis	14 (7.9%)
Upper respiratory tract infection	18 (10.1%)
Investigations	
Weight decreased	16 (9.0%)
Weight increased	9 (5.1%)
Metabolism and nutrition disorders	
Decreased appetite	26 (14.6%)
Nervous system disorders	
Headache	27 (15.2%)
Psychiatric disorders	
Insomnia[a]	27 (15.2%)
Irritability	10 (5.6%)

[a] Insomnia includes TEAEs reported for "insomnia", "initial insomnia", and "middle insomnia"

8.3 Less Common Clinical Trial Adverse Reactions

Uncommon TEAEs (incidence less than 1% and not already reported above in the controlled trials or 6-month open label trial in adults):

- **Blood and lymphatic system:** Neutropenia
- **Cardiac disorders:** Bradycardia, conduction disorder, supraventricular extrasystoles, sinus tachycardia
- **Ear and labyrinth disorders:** Ear discomfort, ear pain, tinnitus, vertigo
- **Eye disorders:** Blepharospasm, dry eye, eye irritation, eye pain, eye pruritus, lacrimation increased
- **Gastrointestinal disorders:** Abdominal pain, aphthous ulcer, constipation, defecation urgency, dental discomfort, eructation, flatulence, frequent bowel movements, gastritis, hematochezia, hemorrhoids, hiatus hernia, irritable bowel syndrome, lip dry, lip swelling

- **General disorders and administration site conditions:** Asthenia, chest discomfort, early satiety, energy increased, facial pain, medical device pain, non-cardiac chest pain, pain, pyrexia
- **Immune system disorders:** Allergy to arthropod sting, drug hypersensitivity, seasonal allergy
- **Infections and infestations:** Bacterial vaginosis, bronchitis, cellulitis, gastroenteritis, gastroenteritis viral, oral herpes, pharyngitis streptococcal, upper respiratory tract infection
- **Injury, poisoning and procedural complications:** Arthropod bite, exposure to communicable disease, foot fracture, ligament sprain, muscle strain, venomous sting
- **Investigations:** Gamma-glutamyltransferase increased, aspartate aminotransferase increased, blood urine present, weight increased
- **Musculoskeletal and connective tissue disorders:** Arthralgia, muscle spasms, muscle twitching, osteoarthritis, pain in extremity, temporomandibular joint syndrome
- **Neoplasms benign, malignant and unspecified (include cysts and polyps):** Uterine cancer
- **Nervous system disorders:** Aphasia, balance disorder, disturbance in attention, dizziness postural, dysesthesia, hyperreflexia, hypersomnia, hypoesthesia, mental impairment, memory impairment, migraine, neuralgia, oromandibular dystonia, restless legs syndrome, sensory disturbance, sleep paralysis, taste disorder, tremor, tunnel vision
- **Psychiatric disorders:** Abnormal dreams, affect liability, blunted affect, confusional state, depressed mood, dermatillomania, dysphoria, euphoric mood, flat affect, hypnopompic hallucination, mental fatigue, mood altered, mood swings, nervousness, nightmare, orgasm abnormal, paranoia, psychotic disorder, tearfulness, terminal insomnia
- **Renal and urinary disorders:** Calculus urinary, micturition urgency, nephrolithiasis, pollakiuria, polyuria
- **Reproductive system and breast disorders:** Erectile dysfunction, metrorrhagia, vaginal hemorrhage
- **Respiratory, thoracic and mediastinal disorders:** Dyspnea, dyspnea exertional, epistaxis, nasal dryness, nasal congestion, rhinorrhea, throat clearing
- **Skin and subcutaneous tissue disorders**: Acne, dry skin, night sweats, pruritus, rash, rosacea, urticaria
- **Vascular disorders:** Flushing, hot flush, hypertension

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Uncommon TEAEs (incidence less than 1% and not already reported above in the controlled trials or 6-month open label trial in adolescents [12 to 17 years old]):

- **Cardiac disorders:** Palpitations, sinus arrhythmia
- **Ear and labyrinth disorders:** Ear pain, motion sickness
- **Eye disorders:** Dry eye, lacrimation increased
- **Gastrointestinal disorders:** Abdominal discomfort, constipation, diarrhoea, dyspepsia, dental caries, flatulence, lip swelling

- **General disorders and administration site conditions:** Crying, energy increased, feeling jittery, influenza like illness, medical device pain, pyrexia, temperature intolerance, thirst
- **Immune system disorders:** Allergy to animal
- **Infections and infestations:** Bronchitis, gastroenteritis, gastroenteritis viral, hand-foot-and-mouth disease, impetigo, labyrinthitis, otis media, pharyngitis, pharyngitis streptococcal, pneumonia, urinary tract infection, viraemia, viral upper respiratory tract infection
- **Injury, poisoning and procedural complications:** Arthropod bite, excoriation, fall, hand fracture, head injury, joint injury, multiple injuries, muscle injury, muscle strain, scratch
- **Investigations:** Blood creatine phosphokinase increased, blood pressure systolic decreased, blood pressure systolic increased, electrocardiogram PR prolongation, electrocardiogram P wave abnormal, electrocardiogram repolarisation abnormality, heart rate decreased
- **Metabolism and nutrition disorders:** increased appetite
- **Musculoskeletal and connective tissue disorders:** Arthralgia, back pain, muscle tightness, muscle twitching, musculoskeletal chest pain, osteochondrosis, pain in extremity
- **Nervous system disorders:** Dizziness postural, dysarthria, paraesthesia, somnolence, syncope, tremor
- **Psychiatric disorders:** Abnormal behaviour, abnormal dreams, abulia, agitation, anger, blunted affect, confusional state, delirium, depressed mood, dermatillomania, dysphoria, emotional disorder, hypnopompic hallucination, mood swings, panic attack, restlessness, sexually inappropriate behaviour, sleep terror, social avoidant behaviour, suicidal ideation, tearfulness
- **Reproductive system and breast disorders:** Dysmenorrhea
- **Respiratory, thoracic and mediastinal disorders:** Allergic sinusitis, dyspnoea, epistaxis, increased upper airway secretion, nasal congestion, productive cough, sinus congestion, vasomotor rhinitis
- **Skin and subcutaneous tissue disorders**: Dermatitis allergic, erythema, miliaria, pityriasis rosea, rash

8.5 Post-Market Adverse Reactions

- **Suicidal Behaviour and Ideation:**

  There have been post-marketing reports of suicide-related events, including completed suicide, suicide attempt, and suicidal ideation in patients treated with ADHD drugs. In some of these reports, comorbid conditions may have contributed to the event (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Suicidal Behaviour and Ideation).

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

  Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include skin rash, fever, epistaxis, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, thrombocytopenic purpura, angioedema and anaphylactic reaction, photosensitivity reaction, skin discoloration, skin odor abnormal, anorexia, muscle cramps, trismus, convulsions, choreoathetoid movements, dyskinesia, malaise, rebound effect, akathisia, presyncope, somnambulism, speech disorder, syncope, dysphemia, euphoric mood, visual impairment, visual disturbance, difficulties in

accommodation, ear disorder, incontinence, drowsiness, pulse changes, peripheral vascular disease, vasodilation, cardiac arrhythmias, sudden cardiac death, angina, ECG QT prolongation, anger, change in sustained attention, crying, depersonalization, dermatillomania, hallucination (sometimes visual, auditory and/or tactile), impulsive behaviour, logorrhea, obsessive–compulsive disorder, neurosis, onychophagia, oppositional defiant disorder, self-injurious behaviour, suicide attempt, completed suicide, stereotypy, thinking abnormal, accidental injury, anemia, aplastic anemia and pancytopenia, leucopenia, thrombocytopenia, and hypoglycemia. There have been rare reports of Tourette's syndrome and rhabdomyolysis. Toxic psychosis has been reported.

Although a definite causal relationship has not been established, the following have been reported in patients taking other methylphenidate products: instances of abnormal liver function, (e.g., hepatic coma); isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; 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 2 CONTRAINDICATIONS, 9.4 Drug-Drug Interactions, Monoamine Oxidase Inhibitors • Co-Administration of Clonidine; see 9.4 Drug-Drug Interactions, Clonidine

9.2 Drug Interactions Overview

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

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 FOQUEST therapy should be advised to avoid alcohol during treatment.

  In an in vitro dissolution study, there was no increase in the rate of release of methylphenidate from FOQUEST 70 mg capsules with an alcohol concentration of 20% and there was a 71% release of methylphenidate with a 40% alcohol concentration in 2 hours.

  However, in an in vivo alcohol interaction study, in fasted healthy adults, FOQUEST 70 mg capsules

with 40% alcohol concentration resulted in a 1.4-fold increase in the peak plasma methylphenidate concentration and a 1.3-fold increase in the extent of absorption.

9.4 Drug-Drug Interactions

- **Inhibition of Drug Metabolism by Methylphenidate:**

  Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of:

  - coumarin anticoagulants (e.g., warfarin),
  - anticonvulsants (e.g., phenobarbital, phenytoin, primidone) and
  - some antidepressants (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:**

  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 FOQUEST (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, FOQUEST may be associated with pharmacodynamic interactions when co-administered with some antipsychotics. Caution is warranted in patients receiving both FOQUEST 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 FOQUEST, with concomitant use of serotonergic drugs. If concomitant treatment with FOQUEST 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, FOQUEST (and serotonergic drugs) must be immediately discontinued and appropriate treatment instituted.

9.5 Drug-Food Interactions

A pharmacokinetic study demonstrated no significant differences in the rate and extent of absorption in patients under fed or fasted conditions (see 10.3 Pharmacokinetics, Absorption).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Methylphenidate is a 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 stereoisomers. The d isomer is pharmacologically active; the l-isomer has little pharmacologic activity. 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.

FOQUEST is a once-daily, modified-release methylphenidate preparation which utilizes multilayer release (MLR® bead technology), where 20% of the total methylphenidate dose is contained within the immediate release layer and 80% is contained in the delayed controlled release layers, a formulation that demonstrates a biphasic plasma concentration-time profile of methylphenidate release.

Safety Pharmacology: An in vivo study conducted using conscious dogs showed no ECG changes (blood pressure and heart rate) in the cardiovascular system with orally administered doses of

methylphenidate up to 10 mg/kg. Furthermore, in an in vitro study where methylphenidate was applied to either isolated guinea-pig papillary muscle or hERG transfected cells, it showed no effects on the electrophysiological parameters with concentrations of up to 1 µg/mL.

10.3 Pharmacokinetics

Studies in human, rats, mice, dogs, and monkeys demonstrated that methylphenidate is readily absorbed, distributed, metabolized, and eliminated. While some differences in the metabolic pathway were observed amongst different species, the overall metabolic rates were similar. Studies in rats and humans have shown that methylphenidate binds substantially to tissues and is mainly distributed in the striatum of the brain. Biotransformation in the gut or first-pass metabolism, or both, is common among the species studied. The primary metabolic pathway in humans is via deesterification by nonmicrosomal hydrolytic esterases, producing the inactive metabolite, ritalinic acid. Conversely, rats and dogs undergo methylphenidate microsomal oxidation and aromatic hydroxylation in addition to de-esterification. Across all species studied, methylphenidate is primarily excreted from the body via urinary excretion in the form of ritalinic acid.

Absorption

FOQUEST contains beads consisting of multiple layers of drug and drug release-controlling excipients. Each bead consists of multiple concentric layers of drug with 20% of the total methylphenidate dose contained in an immediate release layer and 80% contained in delayed controlled release layers. Methylphenidate is readily absorbed. Following oral administration of a single dose of 35 mg, 55 mg, or 85 mg of FOQUEST in 18 children aged 6 to 12 years, under fasted conditions, plasma methylphenidate concentrations increase rapidly, reaching an initial peak between 1.5 and 2.0 hours followed by gradual ascending concentrations resulting in a second peak between 9 and 11 hours. In adolescents under fasting conditions, plasma methylphenidate concentration reaches an initial peak at about 2 hours (range 1 to 4 hours), followed by a decrease and then a gradual ascending concentration resulting in a second peak at about 11 hours (range 7.5 to 14 hours). In adults under fasted conditions, plasma methylphenidate concentration reaches an initial peak at about 1.6 hours (range 1 to 4 hours), followed by a decrease and then a gradual ascending concentration resulting in a second peak at about 12.5 hours (range 11 to 16 hours). FOQUEST once daily reduces the fluctuations between peak and trough concentrations associated with multiple doses of immediate release methylphenidate treatments.

A 4-way, single dose, crossover study of FOQUEST controlled release capsules (100 mg once daily) and immediate release methylphenidate tablets (20 mg t.i.d, given at 0, 4, and 8 hours) in healthy adults (≥18 years of age) under fed and fasted conditions was completed. Results demonstrated that the rate and extent of absorption of methylphenidate were lower for FOQUEST when dose-normalized and compared to immediate release methylphenidate tablets.

Results demonstrate that food does not significantly affect the observed AUC and Cmax of methylphenidate in healthy adults after single dose oral administration of 100 mg of FOQUEST. The pharmacokinetic data are presented in Table 9.

Table 9: Summary of FOQUEST Pharmacokinetic Parameters for d Methylphenidate in Healthy Adults (≥18 years of age) Following Single Dose Administration under Fasted and Fed Conditions (Mean ± SD)

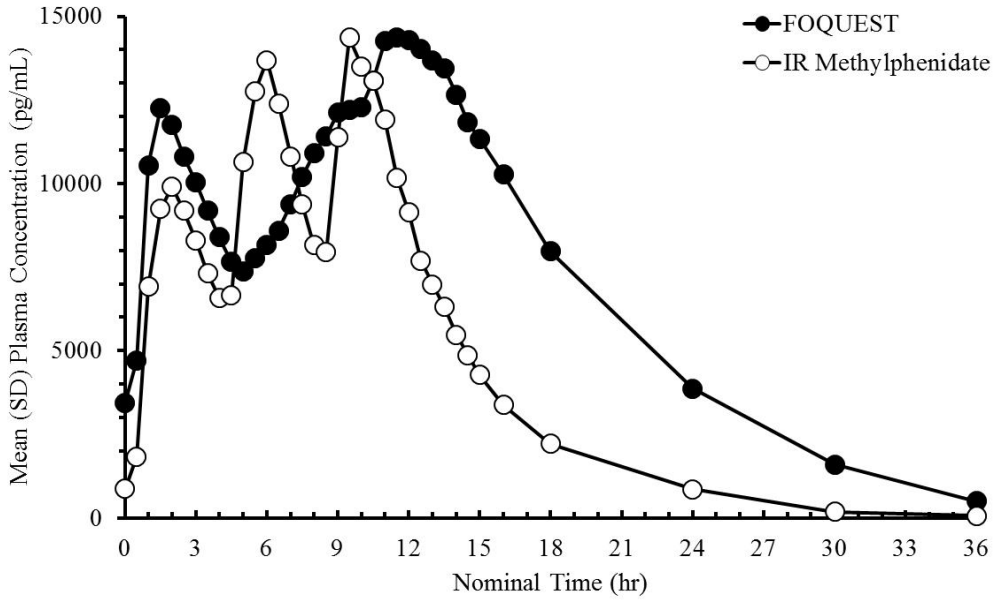
Parameters	Fasted	Fed
	FOQUEST (100 mg once daily) n = 27	**FOQUEST (100 mg once daily) n = 27**
AUC_{0-t} (h*pg/mL)	167783.86 ± 46487.66	161271.48 ± 40500.38
AUC_{0-inf} (h*pg/mL)	205610.43 ± 61472.88	202964.28 ± 57449.88
C_{max} (pg/mL)	12875.81 ± 4590.85	11088.11 ± 2699.06
T_{max} (hr)	11.5[a] (1 – 14.5)	12.5[a] (1.5 – 16.0)
$T_{½\ el}$ (hr)	6.95 ± 3.25	7.03 ± 2.28

[a] Median (Range)

- **Steady State**

  A randomized, 2-way crossover study of FOQUEST controlled release capsules (100 mg once daily) and immediate release methylphenidate tablets (20 mg t.i.d, given at 0, 4, and 8 hours) under fasted conditions administered for 5 consecutive days was conducted in healthy subjects. Lack of statistically significant changes in pre-dose d-methylphenidate concentrations over time (Days 3, 4, and 5) suggest that steady-state conditions were reached. No further accumulation of methylphenidate was observed. Based on dose normalised results, the total drug exposure (AUC0-24h) after dosing with FOQUEST is slightly lower (11.4%) to that obtained following dosing with Ritalin®, with a 40.7% lower concentration peak (Cmax) for FOQUEST. The lower fluctuation index (FI) leads to fewer peaks and troughs and a smaller difference in methylphenidate plasma concentrations between peaks and troughs for patients. The pharmacokinetic data are shown graphically in Figure 1.

Figure 1: Mean Steady State Plasma Concentration-Time Profile of d-Methylphenidate for FOQUEST (100 mg once daily) and Immediate Release Methylphenidate (20 mg t.i.d) at Day 5



- **Sprinkle**

  A 4-way crossover comparative study was completed to evaluate the rate and extent of methylphenidate absorption from FOQUEST (100 mg once daily) under fasting conditions when administered as an intact capsule versus when sprinkled on one tablespoon (15 mL) of soft foods under the following conditions: cold (4°C) applesauce, cold (4°C) yogurt, and frozen (-10°C) ice cream for up to 10 minutes. Results demonstrate that the rate and extent of absorption of methylphenidate are comparable when administered intact and sprinkled on food.

Distribution:

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

Metabolism:

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

Elimination

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

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of methylphenidate after FOQUEST administration were studied

in fasting children with ADHD between 6 and 11 years of age. Results demonstrated that the pharmacokinetic profile in children is comparable to the pharmacokinetic profile in adults and adolescents based on adjustment for body-weight.

- **Geriatrics:** Specific studies of FOQUEST in geriatric patients have not been conducted.
- **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:** FOQUEST has not been studied in patients with hepatic insufficiency.
- **Renal Insufficiency:** There is limited experience with the use of methylphenidate in patients with renal insufficiency. 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 ritalinic acid metabolite. Since renal clearance is not a significant contributor to methylphenidate elimination, and ritalinic acid is an inactive metabolite, renal insufficiency is expected to have little effect on the pharmacokinetics of FOQUEST.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C). Protect from moisture.

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

FOQUEST should be kept in a safe place, such as under lock and out of the sight and reach of children before, during and after use. FOQUEST should not be used in front of children, since they may copy these actions.

Unused or expired FOQUEST should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. FOQUEST should not be shared with others and steps should be taken to protect it from theft or misuse. The patient should speak to their pharmacist about temporary storage options, if required, until the medication can be returned to the pharmacy for safe disposal.

FOQUEST should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

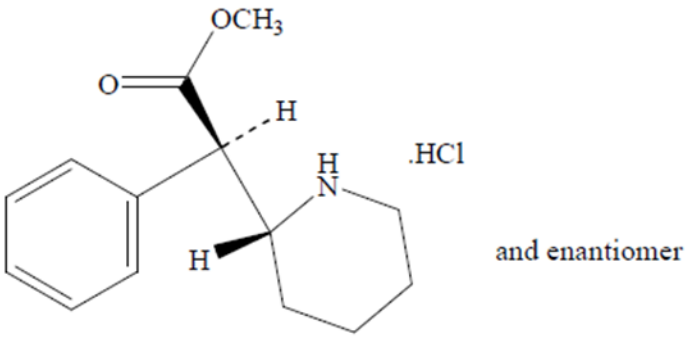
Proper name: methylphenidate hydrochloride

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

Molecular formula and molecular mass: $C_{14}H_{19}NO_2$ • HCl / 269.77

Structural formula:

Figure 2: Structural Formula – methylphenidate hydrochloride



Physicochemical properties: Methylphenidate hydrochloride is a white to off-white, odourless crystalline powder. The pH of the aqueous solution is acidic to litmus, with a pKa of 8.8. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. It has a melting point in the range of 224 – 226°C.

14 CLINICAL TRIALS

FOQUEST® (methylphenidate hydrochloride controlled release capsules) was studied in four double-blind, active- and placebo-controlled studies involving children (>6-11 years of age), adolescents (12-17 years of age) and adults, who met the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Illness, 5th edition (DSM-5) criteria for ADHD. The primary efficacy outcomes in each clinical trial were supported by the secondary endpoints, and data from clinical trials support that once-daily administration of FOQUEST, in the morning, improves efficacy based on behavioural (SKAMP scores) and cognitive (PERMP scores) measures in children over 6 years of age and adults, respectively, with improvements in these measures observed within 1 hour and maintained over 13-16 hours.

14.1 Clinical Trials by Indication

Attention-Deficit Hyperactivity Disorder (ADHD)

Table 10: Summary of patient demographics for clinical trials in ADHD

Study #	Study design	Dosage, route of administration and duration	Study subjects* (n)	Mean age (Range)	Sex	Primary Efficacy Endpoint
Pivotal Trial in Children (6 to 12 years of age)						
063-015	Double-blind, randomized, placebo-controlled, parallel-arm, fixed dose, multi-centre trial measuring efficacy and safety	Oral administration of 25 mg, 35 mg, 45 mg, 55 mg, 70 mg or 85 mg FOQUEST capsules once daily for up to 6 weeks followed by 1 week of double-blind placebo or FOQUEST capsules	**Dose Optimization Period** FOQUEST: n = 156‡ **Double-Blind Period (Laboratory Classroom)** FOQUEST: n = 75 Placebo: n = 73	9.4 (6-12)	F = 54 M = 102	SKAMP-C score
Pivotal Trial in Adolescents (12 to 17 years of age)						
063-009	Double-blind, randomized, placebo-controlled, parallel-arm, fixed dose, multi-centre trial measuring efficacy and safety	Oral administration of placebo, 25 mg, 45 mg, 70 mg or 85 mg FOQUEST capsules once daily for up to 4 weeks	FOQUEST: n = 283 Placebo: n = 71	14.2 (12-17)	F = 115 M = 239	ADHD-5-RS
Pivotal Trial in Adults (≥18 years of age)						
063-010	Double-blind, randomized, placebo-controlled, parallel-arm, fixed dose, multi-centre trial measuring efficacy and safety	Oral administration of placebo, 25 mg, 45 mg, 70 mg or 100 mg FOQUEST capsules once daily for up to 4 weeks	FOQUEST: n = 297 Placebo: n = 78	36.0 (18-72)	F = 198 M = 177	ADHD-5-RS

Study #	Study design	Dosage, route of administration and duration	Study subjects* (n)	Mean age (Range)	Sex	Primary Efficacy Endpoint
Post Market Trial in Adults (≥18 years of age)						
063-020	Double-blind, randomized, placebo-controlled, parallel-arm, fixed dose, multi-centre trial measuring efficacy and safety	Oral administration of 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg or 100 mg FOQUEST capsules once daily for up to 7 weeks followed by 1 week of double-blind placebo or **FOQUEST** capsules	**Dose Optimization Period** FOQUEST: n = 285 **Double-Blind Period (Adult Laboratory Classroom)** FOQUEST: n = 121 Placebo: n = 118	33.2 (18-60)	F = 156 M = 129	PERMP-Total Score

Abbreviations: ADHD-5-RS = Investigator ADHD Rating Scale; SKAMP-C = Swanson, Kotkin, Agler, M-Flynn and Pelham-Combined. *Full analysis population; ǂ total number of randomized subjects who received at least one dose of FOQUEST; PERMP=Permanent Product Measure of Performance

Children:

The efficacy of FOQUEST was evaluated in a laboratory classroom trial conducted in 156 children (aged 6 to 12 years) who met the DSM-5 criteria for ADHD, of which 147 completed the trial. Following washout of previous ADHD medications, there was an open-label dose optimization period (up to 6 weeks) and all patients received an initial FOQUEST dose of 25 mg once daily in the morning. Thereafter the dose was titrated once weekly from 25 mg to 35 mg to 45 mg to 55 mg to 70 mg to 85 mg until an optimal dose was reached. Optimized subjects then entered a one-week randomized, double-blind treatment with FOQUEST or placebo. At the end of this week, raters evaluated the attention and behavior of the subjects in a laboratory classroom setting using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale. SKAMP is a 13-item 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 difference between FOQUEST and placebo in mean SKAMP-Combined score across the entire laboratory classroom trial. The key secondary efficacy endpoints were onset and duration of clinical effect. The treatment difference SKAMP-Combined scores at post-dose time points (1, 2, 4, 6, 8, 10, 12 and 13 hours) were used to evaluate the key secondary efficacy endpoints. The LS mean difference in SKAMP-Combined scores was statistically significantly lower (demonstrating improvement) with FOQUEST compared to placebo from hour 1 through to hour 13. FOQUEST was shown to have an onset of action within 1 hour and a duration of action of 13 hours in children. Results from the one-week double-blind portion of the trial are summarized in Table 11.

Table 11: Results of Trial 063-015 in Children (6 to 12 years of age) with ADHD

Primary Endpoints	Associated value and statistical significance		
		FOQUEST n = 74	**Placebo n = 73**
SKAMP-C	**LS Mean (SE)**	10.3 (0.74)	18.9 (0.73)
	LS Mean Difference (SE) [a]	-8.6 (1.02)	
	95% CI	(-10.6 to -6.6)	
	Statistical Significance:	p < 0.0001	

Abbreviations: SE: standard error; LS Mean: least-squares mean; CI: confidence interval

[a] Difference (drug minus placebo) in least-square mean change from pre-dose

Adolescents:

The safety and efficacy of FOQUEST were assessed in a randomized, double-blind, multicenter, placebo-controlled trial involving 354 adolescent patients (12 to 17 years of age) who met the DSM-5 criteria for ADHD. Following a one-week washout/baseline, patients were titrated to a randomized fixed dose (placebo, 25, 45, 70 or 85 mg) over a two-week period and maintained on the fixed dose for an additional two-week double-blind phase. At the end of the four weeks of double-blind treatment, the mean investigator ADHD rating scale (ADHD-5-RS) score across all doses of FOQUEST was significantly (p = 0.0067) improved relative to placebo.

Table 12: Results of Trial 063-009 in Adolescents (12 to 17 years of age) with ADHD

Primary Endpoints	Associated value and statistical significance		
		FOQUEST n = 283	**Placebo n = 71**
ADHD-5-RS	**Mean Baseline:**	37.08 ± 8.44	37.3 ± 8.40
	LS Mean Change from Baseline:	-15.17	-10.98
	LS Mean Difference from Placebo	-4.2	--
	Statistical Significance:	p = 0.0067	

Abbreviations: LS = Least Square; ADHD-5-RS = Investigator ADHD Rating Scale

Adults:

In a randomized, double-blind, multicentre, placebo-controlled trial involving 375 adult patients (18 to 72 years of age) who met the DSM-5 criteria for ADHD, FOQUEST was demonstrated to be safe and

effective in the treatment of adults with ADHD (Table 13). Following a one-week washout/baseline, patients were titrated to a randomized fixed dose over a two-week period in a double-blind manner and maintained on the assigned fixed dose for an additional two-week double-blind phase. At the end of the four week treatment, the mean investigator ADHD rating scale (ADHD-5-RS) score across all doses of FOQUEST was significantly improved relative to placebo. Improvement in ADHD symptomatology in the ADHD-5-RS total score demonstrated in the primary efficacy analysis (Table 13) was supported by the results of the ADHD-5-RS hyperactivity/impulsivity and inattentiveness subscale analyses, the clinician-rated global improvement (CGI-Improvement) score, the Weiss Functional Impairment Rating Scale (WFIRS-S), the Behaviour Rating Inventory of Executive Function – Adult (BRIEF-A) and the Adult ADHD Quality of Life Scale (AAQoL).

Table 13: Results of Trial 063-010 in Adults (≥18 years of age) with ADHD

Primary Endpoints	**Associated value and statistical significance**		
		FOQUEST n = 297	**Placebo n = 78**
ADHD-5-RS	**Mean Baseline:**	36.3 ± 7.68	37.0 ± 7.94
	LS Mean Change from Baseline:	-14.49	-9.82
	LS Mean Difference from Placebo	-4.7	--
	Statistical Significance:	p=0.0026	

Abbreviations: LS = Least Square; ADHD-5-RS = Investigator ADHD Rating Scale

The efficacy of FOQUEST was also evaluated in a laboratory classroom trial conducted in 285 adults (aged 18 to 60 years) who met the DSM-5 criteria for ADHD. Following an open-label dose optimization period (up to 7 weeks, dose titration ranged from 25 mg to 100 mg) subjects then entered a one-week randomized, double-blind treatment with FOQUEST or placebo. At the end of this week, subjects completed an age-adjusted math test assessment in a laboratory classroom setting using the Permanent Product Measure of Performance (PERMP) test. The PERMP Total score is the sum of the number of math problems attempted plus the number of math problems answered correctly in a 10-minute session with scores ranging from 0-800 with higher scores indicating better performance.

The primary efficacy endpoint was the difference between FOQUEST and placebo in mean PERMP Total score across the entire laboratory classroom trial. The key secondary efficacy endpoints were onset and duration of clinical effect. The LS mean difference in PERMP Total scores was statistically significantly higher with FOQUEST compared to placebo demonstrating an onset of action within 1 hour and a duration of action of 16 hours in adults. Results from the one-week double-blind portion of the trial are summarized in Table 14.

Table 14: Results of Trial 063-020 in Adults ≥ 18 Years of Age with ADHD

		Associated value and statistical significance for Drug at specific dosages			
Primary Endpoint		**FOQUEST n = 116**		**Placebo n = 113**	
PERMP Total Score[b] (LS mean (SE) score over all post-dose timepoints	**LS Mean**	302.9 (3.50)		286.6 (3.52)	
	LS Mean Difference from Placebo (SE)	16.3 (4.39)			
	95% Confidence Intervals	(7.6 to 24.9)			
	Statistical Significance	p = <0.05			
Secondary Endpoint					
PERMP Total Score* (LS mean (SE) score at each post-dose time point) *[Pre-specified Key Secondary Outcome]*					
		Hour 0.5	289.7 (3.71)	Hour 0.5	286.4 (3.72)
		Hour 1*	297.5 (4.12)	Hour 1	284.1 (4.16)
		Hour 2*	309.2 (3.71)	Hour 2	288.9 (3.74)
		Hour 4*	297.0 (4.11)	Hour 4	282.5 (4.15)
		Hour 6*	303.4 (4.41)	Hour 6	286.4 (4.46)
		Hour 7.5*	301.2 (4.24)	Hour 7.5	282.9 (4.28)
		Hour 9*	303.7 (4.34)	Hour 9	286.3 (4.38)
		Hour 11*	305.6 (4.33)	Hour 11	284.1 (4.37)
		Hour 13*	311.8 (4.38)	Hour 13	291.3 (4.42)
		Hour 14*	309.7 (4.69)	Hour 14	295.2 (4.74)
		Hour 15*	302.6 (4.69)	Hour 15	286.4 (4.74)
		Hour 16*	302.8 (5.48)	Hour 16	284.9 (5.55)
		(FOQUEST vs placebo, * p <0.05)			

a. FOQUEST was administered as a single, optimized, morning dose.
b. Higher PERMP total score indicates improvement

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity:

Toxicology and carcinogenesis studies with methylphenidate hydrochloride were performed in rats and mice. Methylphenidate was administered for 2 years at doses of 0, 100, 500 or 1,000 ppm in the feed of rats and 0, 50, 250 and 500 ppm to mice. The average amount of methylphenidate consumed per day was estimated to be 4 to 47 mg/kg/day for rats and 5 to 67 mg/kg/day for mice. An increase of benign tumours of the liver, and increased liver weights, were observed in mice at the high dose. Increased incidences of neoplasms were not seen in the rats.

Genotoxicity:

Methylphenidate was not mutagenic in the Salmonella assay system.

Reproductive and Developmental Toxicology:

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

In animal studies, no teratogenic effects were seen in rats when given at a dose of 75 mg/kg/day, which are 62.5 and 13.5 times the maximum recommended human dose on a mg/kg and mg/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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

FOQUEST®

Methylphenidate hydrochloride controlled release Capsules

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

Serious Warnings and Precautions

- **Drug Dependence**

  Like other stimulants, FOQUEST has the potential to be abused. This can lead you to becoming dependant on FOQUEST or feeling like you need to take more of it over time. Abuse of FOQUEST can lead to dependence.

What is FOQUEST used for?

- FOQUEST is a once-daily treatment for Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years of age and older.

FOQUEST is NOT recommended for use in children under 6 years of age.

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

How does FOQUEST work?

FOQUEST contains methylphenidate hydrochloride, which 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 FOQUEST?

Medicinal ingredients: methylphenidate hydrochloride

Non-medicinal ingredients: ammonio methacrylate copolymer dispersion (type B), anionic copolymer (consisting of methyl acrylate, methyl methacrylate and methacrylic acid), glyceryl monostearate, hypromellose, poylethylene glycol, polysorbate, silicon dioxide, sodium hydroxide, sodium lauryl sulfate, sorbic acid, sugar spheres, and triethyl citrate

In addition, the capsule shells contain the following non-medicinal ingredients:

- 25 mg: FD&C Blue No. 1
- 35 mg: FD&C Yellow No. 6, Titanium Dioxide
- 45 mg: FD&C Yellow No. 5, Titanium Dioxide

- 55 mg: FD&C Blue No. 1, Titanium Dioxide, Yellow Iron Oxide
- 70 mg: Black Iron Oxide, Titanium Dioxide
- 85 mg: Titanium Dioxide
- 100 mg: Red Iron Oxide, Titanium Dioxide, Yellow Iron Oxide

FOQUEST comes in the following dosage forms:

Controlled release capsules: 25 mg (blue), 35 mg (orange), 45 mg (yellow), 55 mg (light green), 70 mg (iron gray), 85 mg (white), 100 mg (cream)

Do not use FOQUEST if you or your child:

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

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

- have mild high blood pressure, heart problems or heart defects.
- have a family history of sudden cardiac death.
- have thyroid problems.
- have had seizures or abnormal EEGs (measure of brainwave activity).
- do high-intensity exercise or activities.
- have mental health problems or family history of mental health problems, including:
    - anxiety
    - psychosis
    - mania
    - bipolar disorder
    - depression
    - aggression
    - suicide
- drink alcohol or have a history of alcohol abuse. You or your child should not drink alcohol while taking FOQUEST.
- have circulation problems in fingers and toes, including numbness, feeling cold or pain (this is also known as Raynaud's phenomenon).

- are pregnant or plan to become pregnant. FOQUEST should not be used during pregnancy.
- are breastfeeding or plan to breastfeed. FOQUEST can pass through breast milk. You should consult with your or your child's healthcare professional to determine whether to stop breast-feeding or discontinue FOQUEST.
- take other drugs for ADHD or depression.
- have tics (movements or sounds that you cannot control) or Tourette's syndrome, or if someone in your family has tics or Tourette's syndrome.

Other warnings you should know about:

Driving and Using Machines: FOQUEST can affect the ability to drive and use potentially dangerous tools or machinery. You or your child should not drive or use tools or machinery until you know how you or your child respond to FOQUEST.

Dependence and Tolerance: Like other stimulants, FOQUEST has the potential to be abused if not taken correctly which can lead to dependence and tolerance. If you or your child have a history of drug or alcohol abuse, discuss this with your or your child's healthcare professional. Do not change the dose or stop taking FOQUEST without first discussing this with your or your child's healthcare professional. If you stop taking FOQUEST, you will need careful supervision because you may feel very depressed.

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

Heart Related Problems: The following heart related problems have been reported in people taking medicine to treat ADHD like FOQUEST**:**

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

Sudden death has been reported in association with stimulant drugs for ADHD treatment in children with structural heart abnormalities. FOQUEST generally should not be used in children, adolescents or adults with known structural heart abnormalities.

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

Your healthcare professional will check:

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

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

Mental Health Problems: The following mental health problems have been reported in people taking medicine to treat ADHD like FOQUEST**:**

- New or worse thoughts or feelings of suicide (thinking about or feeling like killing yourself) 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
- New psychotic symptoms (such as hearing voices, believing things that are not true, being suspicious)

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

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

Serotonin toxicity (also known as Serotonin Syndrome): Serotonin toxicity is a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take FOQUEST 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.

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

Serious Drug Interactions

Do not take FOQUEST if you:

- are taking or have recently taken (in the last 14 days) any MAOIs such as phenelzine, tranylcypromine, or moclobemide as you may have serious side effects.

Taking FOQUEST and clonidine (used to treat ADHD) may cause serious side effects or sudden death.

The following may interact with FOQUEST:

- Alcohol should be avoided, including any medications containing alcohol, such as some cough syrups, while taking FOQUEST
- Certain medicines used to treat or prevent blood clot, such as warfarin
- Certain medicines used to treat seizures, such as phenobarbital, phenytoin, or primidone
- Certain medicines for depression and mood disorders, such as Tricyclic Antidepressants (e.g. amitriptyline) and Selective Serotonin Reuptake Inhibitors (SSRIs).

- Certain medicines used to treat high blood pressure
- Medicines used to manage psychosis (antipsychotics)

How to take FOQUEST:

- Your or your child's healthcare professional will decide the dose that is right. Always follow the directions of the healthcare professional and never change the dose or stop taking FOQUEST without first discussing it with your or your child's healthcare professional.
- FOQUEST should be taken once-a-day, with or without food, as soon as possible in the morning as the effects of FOQUEST can last late into the evening and may affect sleep.
- **FOQUEST capsules should be swallowed whole with a full glass of water and must never be crushed or chewed.**
- For patients unable to swallow the capsule, the capsule may be opened and the entire contents sprinkled onto applesauce, ice cream or yogurt. Do not sprinkle in liquids.
- **To sprinkle FOQUEST onto food:**
    1. Measure a tablespoon of applesauce, ice cream or yogurt.
    2. Open the capsule.
    3. Sprinkle the entire contents (beads) onto the tablespoon.
    4. Take the entire mixture **immediately or within 10 minutes.**
    - Do **not** chew the capsule contents (beads).
    - Rinse your or your child's mouth with water and swallow the water.
    - Do **not** keep any of the food/medicine mixture for another dose.
    - Throw out any food/medicine mixture if:
        - it has been more than 10 minutes since you sprinkled the capsule onto the food.
        - you do not remember when you sprinkled the capsule onto the food.
        - you do not remember which food you sprinkled the capsule onto.

Usual dose:

- Take the dose prescribed by your or your child's healthcare professional.
- The starting dose will depend on whether you or your child have already been taking a medication that contains methylphenidate (the ingredient in FOQUEST).
- The healthcare professional may adjust the amount of medicine until it is right for you or your child.
- From time to time, the healthcare professional may interrupt treatment with FOQUEST to check for symptoms while you or your child are not taking the medicine.

- The maximum daily dose for children and adolescents (6 to <18 years old) is 70 mg.
- The maximum daily dose for adults (≥18 years old) is 100 mg.

Overdose:

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

Missed Dose:

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

What are possible side effects from using FOQUEST?

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

Side effects may include:

- Loss of appetite
- Headache
- Insomnia, sleep disorder
- Abdominal pain and discomfort
- Dry mouth
- Diarrhea, nausea, vomiting
- Fatigue, drowsiness
- Feeling jittery, nervousness or anxiety
- Weight loss, weight gain
- Sinus infection, common cold
- Heart rate increase
- Dizziness
- Irritability
- Increased sweating
- Difficulty opening the mouth (trismus)
- Inability to control excretion of urine (incontinence)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Mental Health Problems: • Paranoia, delusions • Hallucinations: seeing, feeling or hearing things that are not real • Mania: feeling unusually excited, or over-active • Depression • Agitation, irritability, anxiety, nervousness • Aggression, hostility • Compulsions		✓	
COMMON			
Heart Problems: fast heartbeat, palpitations, chest pain, difficulty breathing, fainting			✓
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.	✓		
UNKNOWN			
Suicidal Behaviour: thoughts or feelings about harming yourself			✓
Raynaud's Phenomenon: discoloration of the fingers and toes, pain, sensations of cold and/or numbness		✓	
Seizures or Convulsions: loss of consciousness with uncontrollable shaking (fit)			✓
Serious Allergic Reaction: itching, skin rash, swelling of the mouth, face, lips, or tongue, trouble 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		✓	
Tourette's Syndrome: motor tics (hard-to-control, repeated twitching of any part of your body) and verbal tics (hard-to-control repeating of sounds or words)			✓
Edema: swollen hands, ankles or feet	✓		
Nosebleed	✓		

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

Keep unused or expired FOQUEST in a secure place to prevent theft, misuse or accidental exposure. Keep FOQUEST out of sight and reach of children and pets.

Store at room temperature (15°C to 30°C). Protect from moisture.

FOQUEST should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about FOQUEST:

- 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.elvium.ca, or by calling 1-833-744-0005

This leaflet was prepared by Elvium Life Sciences.

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