HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use QUILLICHEW ER™ safely and effectively. See full prescribing information for QUILLICHEW ER.

QUILLICHEW ER™ (methylphenidate hydrochloride) extended-release chewable tablets, for oral use, CII
Initial U.S. Approval: 1955

WARNING: ABUSE AND DEPENDENCE
See full prescribing information for complete boxed warning.

- **CNS stimulants, including QuilliChew ER, have a high potential for abuse and dependence (5.1, 9.2, 9.3)**
- **Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)**

----------RECENT MAJOR CHANGES ----------
Dosage and Administration (2.2) ……3/2017

----------INDICATIONS AND USAGE----------
QuilliChew ER is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). (1)

----------DOSAGE AND ADMINISTRATION----------
- QuilliChew ER may be taken with or without food. (2.1)
- For patients 6 years and above, the recommended starting dose is 20 mg given orally once daily in the morning. Dosage may be titrated weekly in increments of 10 mg, 15 mg or 20 mg per day. Daily dosage above 60 mg is not recommended. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- Extended-release chewable tablets: 20 mg and 30 mg of methylphenidate hydrochloride (HCl), functionally scored (3)
- Extended-release chewable tablets: 40 mg of methylphenidate HCl, not scored (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to methylphenidate or product components (4.1)
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days (4.2, 7.1)

----------WARNINGS AND PRECAUTIONS----------
- *Serious Cardiovascular Reactions*: Sudden death has been reported in association with CNS stimulants at recommended doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease. (5.2)
- *Blood Pressure and Heart Rate Increases*: Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic. (5.3)
- *Psychiatric Adverse Reactions*: Use of CNS stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to QuilliChew ER use. (5.4)
- *Priapism*: Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed. (5.5)
- *Peripheral Vasculopathy, including Raynaud's Phenomenon*: CNS stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.6)
- *Long-Term Suppression of Growth*: Monitor height and weight at appropriate intervals in pediatric patients. (5.7)
- *Risks in Phenylketonurics*: QuilliChew ER extended-release chewable tablets contain phenylalanine, a component of aspartame. (5.8)

----------ADVERSE REACTIONS----------
Based on accumulated data from other methylphenidate products, the most common (≥5% and twice the rate of placebo) adverse reactions are appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including QuilliChew ER, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)].*

1 INDICATIONS AND USAGE

QuilliChew ER is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating children, adolescents, and adults with CNS stimulants including QuilliChew ER, assess for the presence of cardiac disease (i.e., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) *[see Warnings and Precautions (5.2)]*.

Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and periodically re-evaluate the need for QuilliChew ER use *[see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9)]*.

2.2 General Dosing Information

The recommended starting dose of QuilliChew ER for patients 6 years and above is 20 mg once daily orally in the morning. The dose may be titrated up or down weekly in increments of 10 mg, 15 mg or 20 mg. The 10 mg and 15 mg doses can each be achieved by breaking in half the functionally scored 20 mg and 30 mg tablets, respectively. Daily doses above 60 mg have not been studied and are not recommended. As with any CNS stimulant, during titration of QuilliChew ER, the prescribed dose should be adjusted, if necessary, until a well-tolerated, therapeutic dose is achieved.

Pharmacological treatment of ADHD may be needed for extended periods. Health care providers should periodically re-evaluate the long-term use of QuilliChew ER, and adjust dosage as needed.

2.3 Administration Instructions

QuilliChew ER should be orally administered once daily in the morning with or without food *[see Clinical Pharmacology (12.3)]*.

2.4 Switching from other Methylphenidate Products

If switching from other methylphenidate products, discontinue that treatment, and titrate with QuilliChew ER using the above titration schedule.

Do not substitute for other methylphenidate products on a milligram-per-milligram basis, because of different methylphenidate base compositions and differing pharmacokinetic profiles *[see Description (11) and Clinical Pharmacology (12.3)]*.

2.5 Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug. QuilliChew ER should be periodically discontinued to assess the child's condition. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

3 DOSAGE FORMS AND STRENGTHS

Extended-release chewable tablets:

20 mg equivalent of methylphenidate HCl available as a speckled, off-white, capsule-shaped coated tablet, debossed with “NP 12” on one side and functionally scored on the other side.

30 mg equivalent of methylphenidate HCl available as a speckled, light pink color, capsule-shaped coated tablet, debossed with “NP 13” on one side and functionally scored on the other side.

40 mg equivalent of methylphenidate HCl available as a speckled, dark pink to peach color, capsule-shaped coated tablet, debossed with “NP 14” on one side and plain (not scored) on the other side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Methylphenidate or other Components of QuilliChew ER

QuilliChew ER is contraindicated in patients known to be hypersensitive to methylphenidate, or other components of QuilliChew ER. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other methylphenidate products *[see Adverse Reactions (6.2)]*.

4.2 Monoamine Oxidase Inhibitors
QuilliChew ER is contraindicated during concomitant treatment with monoamine oxidase inhibitors (MAOIs), and also within 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (MAOI), because of the risk of hypertensive crisis *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence
CNS stimulants, including QuilliChew ER, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy *[see Drug Abuse and Dependence (9.2, 9.3)]*.

5.2 Serious Cardiovascular Reactions
Stroke and myocardial infarction have occurred in adults treated with CNS stimulants at recommended doses. Sudden death has occurred in children and adolescents with structural cardiac abnormalities and other serious cardiac problems, and in adults taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with QuilliChew ER.

5.3 Blood Pressure and Heart Rate Increases
CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). Individuals may have larger increases. Monitor all patients for hypertension and tachycardia.

5.4 Psychiatric Adverse Reactions

Exacerbation of Pre-Existing Psychosis

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

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a manic or mixed episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing QuilliChew ER. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared to 0 in placebo-treated patients.

5.5 Priapism
Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon
CNS stimulants, including QuilliChew ER, used to treat ADHD 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 postmarketing 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 of digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

5.7 Long-Term Suppression of Growth
CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Careful follow-up of weight and height in pediatric patients ages 7 to 10 years who were randomized to either methylphenidate or nonmedication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and nonmedication-treated pediatric patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated pediatric patients (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including QuilliChew ER. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

5.8 Risks in Patients with Phenylketonuria

Phenylalanine can be harmful to patients with phenylketonuria (PKU). QuilliChew ER extended-release chewable tablets contain phenylalanine, a component of aspartame. Each 20 mg, 30 mg, and 40 mg extended-release chewable tablet contains 3 mg, 4.5 mg, and 6 mg phenylalanine, respectively. Before prescribing QuilliChew ER in patients with PKU, consider the combined daily amount of phenylalanine from all sources, including QuilliChew ER.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Known hypersensitivity to methylphenidate products or other ingredients of QuilliChew ER *[see Contraindications (4.1)]*
- Hypertensive Crisis When Used Concomitantly with Monoamine Oxidase Inhibitors *[see Contraindications (4.2), Drug Interactions (7.1)]*
- Drug Dependence *[see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)]*
- Serious Cardiovascular Reactions *[see Warnings and Precautions (5.2)]*
- Blood Pressure and Heart Rate Increases *[see Warnings and Precautions[(5.3)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Priapism *[see Warnings and Precautions (5.5)]*
- Peripheral Vasculopathy, including Raynaud's phenomenon *[see Warnings and Precautions (5.6)]*
- Long-Term Suppression of Growth *[see Warnings and Precautions (5.7)]*
- Risks in Phenylketonuria *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trials Experience with Other Methylphenidate Products in Children, Adolescents, and Adults with ADHD

Commonly reported (≥2% of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: appetite decreased, 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, and pyrexia.

Clinical Trials Experience with QuilliChew ER in Children with ADHD

There is limited experience with QuilliChew ER in controlled trials. The safety data in this section is based on data from a laboratory classroom study conducted in 90 pediatric subjects (ages 6 to 12 years) with ADHD. The study consisted of a 6-week dose optimization period, followed by a randomized, double-blind, parallel group treatment period with the individually optimized dose of QuilliChew ER or placebo.

The most common (≥2% in the QuilliChew ER group and greater than placebo) adverse reactions reported in the double-blind, randomized, placebo-controlled phase in patient optimized to doses of QuilliChew ER 20 to 60 mg/day are described in Table 1.

Table 1. Common Adverse Reactions Occurring in ≥2% of Subjects on QuilliChew ER and Greater than Placebo During the Double-Blind Period of the ADHD Laboratory Classroom Study

Adverse reaction	QuilliChew ER N= 42 n (%)	Placebo N= 44 n (%)
Decreased appetite	1 (2.4)	0 (0)
Aggression	1 (2.4)	0 (0)
Emotional poverty	1 (2.4)	0 (0)
Nausea	1 (2.4)	0 (0)
Headache	1 (2.4)	0 (0)
Weight decreased	1 (2.4)	0 (0)

6.2 Postmarketing Experience

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

Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura
Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystole, Supraventricular tachycardia, Ventricular extrasystole
Eye Disorders: Diplopia, Mydriasis, Visual impairment

General Disorders: Chest pain, Chest discomfort, Hyperpyrexia
Hepatobiliary Disorders: Severe hepatocellular injury
Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions, and Exanthemas NEC
Investigations: Alkaline phosphatase increased, Bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal
Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis
Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia, Serotonin syndrome in combination with serotonergic drugs
Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Libido changes, Mania
Urogenital System: Priapism
Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema
Vascular Disorders: Raynaud's phenomenon

7 DRUG INTERACTIONS

7.1 Clinically Important Drug Interactions

MAO Inhibitors
Do not administer QuilliChew ER concomitantly with monoamine oxidase inhibitors (MAOIs) or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are limited published studies and small case series that report on the use of methylphenidate in pregnant women; however, the data are insufficient to inform any drug-associated risks. There are clinical considerations *[see Clinical Considerations]*. No teratogenic effects were observed in embryo-fetal development studies with oral administration of methylphenidate to pregnant rats and rabbits during organogenesis at doses 2 and 11 times, respectively, the maximum recommended human dose (MRHD). However, spina bifida was observed in rabbits at a dose 40 times the MRHD *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

CNS stimulant medications, such as QuilliChew ER, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

Data

Animal Data

In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 40 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Limited published literature reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. Long-term neurodevelopmental effects on infants from CNS stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for QuilliChew ER and any potential adverse effects on the breastfed infant from QuilliChew ER or from the underlying maternal condition.

Clinical Considerations

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

8.4 Pediatric Use

The safety and effectiveness of QuilliChew ER have been established in pediatric patients ages 6 to 17 years. Use of QuilliChew ER in these age groups is based on one adequate and well-controlled clinical study in pediatric patients 6 to 12 years old, pharmacokinetic data in adolescents and adults, and safety information from other methylphenidate-containing products. The long-term efficacy of methylphenidate in pediatric patients has not been established *[see Clinical Pharmacology (12), Clinical Studies (14)]*. Safety and efficacy in pediatric patients below the age of 6 years have not been established.

Long Term Suppression of Growth

Growth should be monitored during treatment with CNS stimulants, including QuilliChew ER. Children who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.7)]*.

Juvenile Animal Data

Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 6 times the maximum recommended human dose (MRHD) on a mg/m^2 basis.

In the study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal day 7) and continuing through sexual maturity (postnatal week 10). When these animals were tested as adults (postnatal weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was observed in females exposed to the highest dose (12 times the MRHD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use

QuilliChew ER has not been studied in patients over the age of 65 years.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

QuilliChew ER contains methylphenidate, a Schedule II controlled substance.

9.2 Abuse

CNS stimulants including QuilliChew ER, other methylphenidate-containing products, and amphetamines have a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.

Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been observed. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration which can result in overdose and death *[see Overdosage (10)]*.

To reduce the abuse of CNS stimulants including QuilliChew ER, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants *[see How Supplied/Storage and Handling (16.1, 16.2)]*, monitor for signs of abuse while on therapy, and re-evaluate the need for QuilliChew ER use.

9.3 Dependence

Tolerance

Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) can occur during chronic therapy with CNS stimulants including QuilliChew ER.

Dependence

Physical dependence (a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) can occur in patients treated with CNS stimulants including QuilliChew ER. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include dysphoric mood; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

10 OVERDOSAGE

Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice on the management of overdosage with methylphenidate. Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension, tachypnea, mydriasis, dryness of mucous membranes, and rhabdomyolysis.

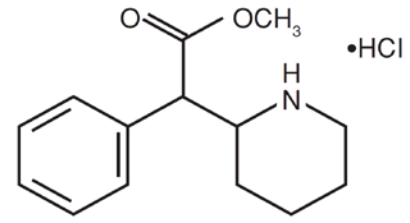
11 DESCRIPTION

QuilliChew ER (methylphenidate hydrochloride extended-release chewable tablets) is available in three dosage strengths - 20 mg, 30 mg and 40 mg. The dosage strengths are expressed in terms of methylphenidate hydrochloride equivalents; however only 15% of methylphenidate is present as methylphenidate hydrochloride salt. The remaining 85% is present as methylphenidate ionically-bound to the sulfonate groups of sodium polystyrene sulfonate particles. QuilliChew ER contains approximately 30% immediate-release and 70% extended-release methylphenidate.

The QuilliChew ER extended-release chewable tablets are cherry flavored.

Methylphenidate HCl is a central nervous system (CNS) stimulant. The chemical name is methyl α-phenyl-2-piperidineacetate hydrochloride, and its structural formula is shown in Figure 1.

Figure 1. Methylphenidate HCl Structure



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

Methylphenidate HCl is a white, odorless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone.

QuilliChew ER also contains the following inactive ingredients: aspartame *[see Warnings and Precautions (5.8)]*, cherry flavor, citric acid, crospovidone, D&C red #30 (for 30 mg strength), D&C red #7 (for 40 mg strength), guar gum, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl acetate, polyvinyl alcohol, povidone, silicon dioxide, sodium polystyrene sulfonate, talc, triacetin, xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate HCl is a central nervous system (CNS) stimulant.

12.2 Pharmacodynamics

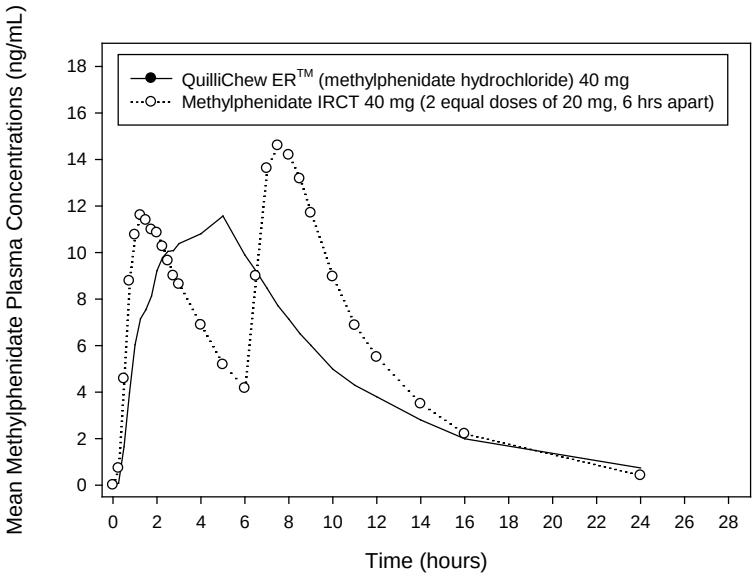
Methylphenidate is a racemic mixture comprised of the *d*- and *l*-isomers. The *d*-isomer is more pharmacologically active than the *l*-isomer. The mode of therapeutic action in ADHD is not known. Methylphenidate blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase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

12.3 Pharmacokinetics

Absorption

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

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



Food Effect

High-fat meal had no effect on the time to peak concentration, and increased C_{max} and systemic exposure (AUC_{inf}) of methylphenidate by about 20% and 4%, respectively, after a single dose administration of 40 mg QuilliChew ER.

Elimination

Plasma methylphenidate concentrations decline monophasically following oral administration of QuilliChew ER. The mean plasma terminal elimination half-life of methylphenidate was about 5.2 hours in healthy volunteers following a single 40 mg dose administration.

Metabolism

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

Excretion

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

Alcohol Effect

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

Specific Populations

Sex

There is insufficient experience with the use of QuilliChew ER to detect gender variations in pharmacokinetics.

Race

There is insufficient experience with the use of QuilliChew ER to detect ethnic variations in pharmacokinetics.

Age

There are no specific pediatric pharmacokinetic studies for QuilliChew ER. However, the pharmacokinetics of methylphenidate in pediatric patients 6 to 17 years old are not expected to be significantly different from adults following QuilliChew ER administration.

Renal Impairment

There is no experience with the use of QuilliChew ER in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPAA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of QuilliChew ER.

Hepatic Impairment

There is no experience with the use of QuilliChew ER in patients with hepatic insufficiency.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 4 times the maximum recommended human dose on a mg/m^2 basis. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

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

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

The efficacy of QuilliChew ER was evaluated in a laboratory classroom study conducted in 90 pediatric subjects (ages 6 to 12 years) with ADHD. Patients in the trial met DSM-IV criteria for ADHD. The study began with a 6-week open-label dose optimization period with an initial QuilliChew ER dose of 20 mg. Patients were instructed to chew each dose once daily in the morning. The dose could be titrated weekly in increments of 10 to 20 mg until a therapeutic dose or the maximum dose of 60 mg/day was reached.

Eighty-six of the 90 enrolled subjects then entered a 1-week randomized, double-blind, parallel group treatment period with the individually optimized dose of QuilliChew ER or placebo. The intent-to-treat (ITT) population consisted of 85 randomized subjects who received at least 1 dose of double-blind study drug and had at least 1 post-Baseline assessment of the primary efficacy variable. At the end of the double-blind treatment period, the laboratory classroom raters and teachers evaluated the attention and behavior of the subjects, throughout the day using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale. The SKAMP rating scale is a validated 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting.

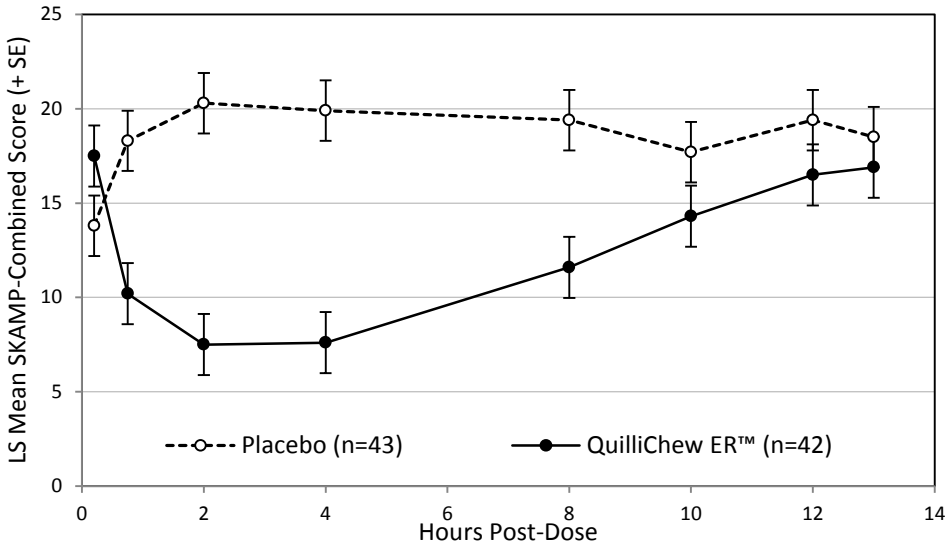
The SKAMP-Combined score, measured at 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose during the laboratory classroom day at the end of the double-blind treatment period, was used to assess the primary and the key secondary efficacy parameters. The primary efficacy endpoint was the average of treatment effects across all the time points as specified above during the classroom day. The key secondary efficacy parameters were onset and duration of clinical effect. QuilliChew ER was statistically significantly superior to placebo with respect to the primary endpoint (Table 2). QuilliChew ER also showed improvement over placebo at 0.75, 2, 4, and 8 hours post-dosing. Efficacy results at each time point are summarized in Figure 3.

Table 2. Primary Efficacy Result (ITT Population)

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

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

Figure 3. SKAMP-Combined Scores Over Time (LS Mean ± SE) by Treatment Group (ITT Population)



ITT: intent-to-treat
LS means from post-dose time-points were obtained from a repeated measures mixed model with terms for center, hour, treatment and treatment by hour interaction. For the pre-dose time-point, arithmetic means and standard errors are displayed.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

QuilliChew ER is supplied as extended-release chewable tablets in 20 mg, 30 mg and 40 mg strengths.

The 20 mg strength extended-release chewable tablet is available as a speckled, off-white, capsule-shaped coated tablet, debossed with "NP 12" on one side and functionally scored on the other side.

The 30 mg strength extended-release chewable tablet is available as a speckled, light pink color, capsule-shaped coated tablet, debossed with "NP 13" on one side and functionally scored on the other side.

The 40 mg strength extended-release chewable tablet is available as a speckled, dark pink to peach color, capsule-shaped coated tablet, debossed with "NP 14" on one side and plain on the other side (not scored).

The product is supplied in bottles of 100.

QuilliChew ER extended-release chewable tablets			
Package Configuration	Tablet Strength (mg)	NDC	Print
Bottles of 100	20 mg	NDC 24478-120-01	NP 12
Bottles of 100	30 mg	NDC 24478-130-01	NP 13
Bottles of 100	40 mg	NDC 24478-140-01	NP 14

16.2 Storage and Handling

Store at 20°C to 25ºC (68°F to 77ºF); excursions permitted from 15ºC to 30ºC (59ºF to 86ºF). [See USP Controlled Room Temperature.]

Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired QuilliChew ER by a medicine take-back program or by an authorized collector registered with the Drug Enforcement Administration. If no take-back program or authorized collector is available, mix QuilliChew ER with an undesirable, nontoxic substance to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and discard QuilliChew ER in the household trash.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Controlled Substance Status/Potential for Abuse and Dependence

Advise patients and their caregivers that QuilliChew ER is a federally controlled substance, and it can be abused and lead to dependence *[see Drug Abuse and Dependence (9.1, 9.2, 9.3)]*. Instruct patients that they should not give QuilliChew ER to anyone else. Advise patients to store QuilliChew ER in a safe place, preferably locked, to prevent abuse. Advise patients to comply with laws and regulations on drug disposal. Advise patients to dispose of remaining, unused, or expired QuilliChew ER through a medicine take-back program if available *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)]*.

Dosage and Administration Instructions

Advise patients that QuilliChew ER should be taken by mouth once daily in the morning with or without food.

Serious Cardiovascular Risks

Advise patients, caregivers, and family members that there is a potential for serious cardiovascular risks including sudden death, myocardial infarction, and stroke with QuilliChew ER use. Instruct patients to contact a health care provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease *[see Warnings and Precautions (5.2)]*.

Blood Pressure and Heart Rate Increases

Advise patients that QuilliChew ER can elevate blood pressure and heart rate *[see Warnings and Precautions (5.3)]*.

Psychiatric Risks

Advise patients that QuilliChew ER, at recommended doses, can cause psychotic or manic symptoms, even in patients without a prior history of psychotic symptoms or mania *[see Warnings and Precautions (5.4)]*.

Priapism

Advise patients, caregivers, and family members of the possibility of painful or prolonged penile erections (priapism). **Instruct the patient to seek immediate medical attention in the event of priapism** *[see Warnings and Precautions (5.5)]*.

Circulation Problems in Fingers and Toes [Peripheral Vasculopathy, including Raynaud's Phenomenon]

- Instruct patients beginning treatment with QuilliChew ER about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change color from pale, to blue, to red.
- Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes.
- **Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking QuilliChew ER.**
- Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients *[see Warnings and Precautions (5.6)]*.

Suppression of Growth

Advise patients, families, and caregivers that QuilliChew ER can cause slowing of growth and weight loss *[see Warnings and Precautions (5.7)]*.

Alcohol Effect

Advise patients to avoid alcohol while taking QuilliChew ER extended-release chewable tablets. Consumption of alcohol while taking QuilliChew ER may result in a more rapid release of the dose of methylphenidate *[see Clinical Pharmacology (12.3)]*.

Risks in Patients with Phenylketonuria (PKU)

Advise patients with phenylketonuria that QuilliChew ER extended-release chewable tablets contain phenylalanine, a component of aspartame *[see Warnings And Precautions (5.8)]*.

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MEDICATION GUIDE

QuilliChew ER™ (quil-ih' CHOO' ee-ahr)
(methylphenidate hydrochloride)
extended-release chewable tablets CII

What is the most important information I should know about QuilliChew ER?

QuilliChew ER is a federally controlled substance (CII) because it can be abused or lead to dependence. Keep QuilliChew ER in a safe place to prevent misuse and abuse. Selling or giving away QuilliChew ER may harm others and is against the law.

Tell your health care provider if you or your child have (or have a family history of) ever abused or been dependent on alcohol, prescription medicines, or street drugs.

The following have been reported with use of methylphenidate hydrochloride and other stimulant medicines.

1. Heart-related problems:

- **sudden death in patients who have heart problems or heart defects**
- **stroke and heart attack in adults**
- **increased blood pressure and heart rate**

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

Your health care provider should check you or your child carefully for heart problems before starting QuilliChew ER.

Your health care provider should check your or your child's blood pressure and heart rate regularly during treatment with QuilliChew ER.
Call your health care provider right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking QuilliChew ER.

2. Mental (Psychiatric) problems:

- **new or worse behavior and thought problems**
- **new or worse bipolar illness**
- **new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms**

Tell your health care provider about any mental problems you or your child have, or about a family history of suicide, bipolar illness, or depression.

Call your health care provider right away if you or your child have any new or worsening mental symptoms or problems while taking QuilliChew ER, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

3. Circulation problems in fingers and toes [Peripheral vasculopathy, including Raynaud's phenomenon]**:**

- Fingers or toes may feel numb, cool, painful
- Fingers or toes may change color from pale, to blue, to red

Tell your health care provider if you have or your child has numbness, pain, skin color change, or sensitivity to temperature in the fingers or toes.

Call your health care provider right away if you have or your child has any signs of unexplained wounds appearing on fingers or toes while taking QuilliChew ER.

What is QuilliChew ER?

QuilliChew ER is a central nervous system stimulant prescription medicine. QuilliChew ER is an extended-release chewable tablet. **It is used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).** QuilliChew ER may help increase attention and decrease impulsiveness and hyperactivity in people with ADHD.

It is not known if QuilliChew ER is safe and effective in children under 6 years of age.

Do not take QuilliChew ER if you or your child:

- are allergic to methylphenidate hydrochloride, or any of the ingredients in QuilliChew ER. See the end of this Medication Guide for a complete list of ingredients in QuilliChew ER.
- are taking or have taken within the past 14 days a type of anti-depression medicine called a monoamine oxidase inhibitor (MAOI).

QuilliChew ER may not be right for you or your child. Before starting QuilliChew ER tell your or your child's health care provider about all health conditions (or a family history of) including:

- heart problems, heart defects, high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- circulation problems in fingers and toes
- phenylketonuria (PKU). QuilliChew ER extended-release chewable tablets contain phenylalanine as part of the artificial sweetener, aspartame. The artificial sweetener may be harmful to people with PKU or who are allergic to phenylalanine.
- if you are pregnant or plan to become pregnant. It is not known if QuilliChew ER will harm your unborn baby. Talk to your health care provider if you are pregnant or plan to become pregnant.
- if you are breastfeeding or plan to breast feed. QuilliChew ER passes into your breast milk. You and your doctor should decide if you will take QuilliChew ER or breastfeed.

Tell your health care provider about all of the medicines that you or your child take including prescription and nonprescription medicines, vitamins, and herbal supplements. QuilliChew ER and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted while taking QuilliChew ER.

Your health care provider will decide whether QuilliChew ER can be taken with other medicines.

Especially tell the health care provider if you or your child takes:

- anti-depression medicines including MAOIs

Know the medicines that you or your child takes. Keep a list of your medicines with you to show your health care provider and pharmacist.

Do not start any new medicine while taking QuilliChew ER without talking to your health care provider first.

How should QuilliChew ER be taken?

- **Read the step-by-step instructions for using QuilliChew ER extended-release chewable tablets at the end of this Medication Guide.**
- Take QuilliChew ER exactly as prescribed. Your health care provider may adjust the dose, if needed, until it is right for you or your child. During dose adjustment, you or your child may still have ADHD symptoms.
- Take QuilliChew ER 1 time each day in the morning. QuilliChew ER is an extended-release chewable tablet that releases medicine into your body throughout the day.
- The 20 mg and 30 mg QuilliChew ER chewable tablets are scored (bisected) and can be cut in half if needed, for you to get the right dose. QuilliChew ER 40mg is not scored (bisected) and cannot be divided.
- QuilliChew ER can be taken with or without food.
- From time to time, your health care provider may stop QuilliChew ER treatment for a while to check ADHD symptoms.
- Your health care provider may do regular checks of the blood, heart, and blood pressure while taking QuilliChew ER.
- Children should have their height and weight checked often while taking QuilliChew ER. QuilliChew ER treatment may be stopped if a problem is found during these check-ups.
- In case of poisoning call your poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.
- If a dose is missed, you or your child should talk to your health care provider about dosing.

What should I avoid while taking QuilliChew ER?

- QuilliChew ER should not be taken with MAOI medicines. Do not start taking QuilliChew ER if you stopped taking an MAOI in the last 14 days.
- Do not drink alcohol while taking QuilliChew ER. This may cause a faster release of your methylphenidate dose.

What are possible side effects of QuilliChew ER?

QuilliChew ER may cause serious side effects, including:

- **See "What is the most important information I should know about QuilliChew ER?"** for information on reported heart and mental problems.

Other serious side effects include:

- painful and prolonged erections (priapism) have occurred with methylphenidate. If you or your child develop priapism seek medical help right away. **Because priapism can cause long lasting damage, it should be checked by a health care provider right away.**
- slowing of growth (height and weight) in children

The most common side effects of QuilliChew ER include:

- decreased appetite
- trouble sleeping
- nausea
- vomiting
- indigestion
- stomach pain
- weight loss
- anxiety
- dizziness
- irritability
- mood swings
- fast heart beat
- increased blood pressure

These are not all the possible side effects of QuilliChew ER.

Call your health care provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store QuilliChew ER?

- Store QuilliChew ER in a safe place at 68°F to 77°F (20°C to 25°C).
- **Keep QuilliChew ER and all medicines out of the reach of children.**

General information about the safe and effective use of QuilliChew ER

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use QuilliChew ER for a condition for which it was not prescribed. Do not give QuilliChew ER to other people, even if they have the same condition. It may harm them.

You can ask your pharmacist or health care provider for information about QuilliChew ER that was written for health care professionals.

What are the ingredients in QuilliChew ER?

Active Ingredient: methylphenidate
Inactive Ingredients: aspartame , cherry flavor, citric acid, crospovidone, D&C red #30 (for 30 mg strength), D&C red #7 (for 40 mg strength), guar gum, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl acetate, polyvinyl alcohol, povidone, silicon dioxide, sodium polystyrene sulfonate, talc, triacetin, xanthan gum.

For more information, please contact Pfizer, Inc. at 1-800-438-1985 or visit the website at www.QuilliChewER.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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