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## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use QUILLIVANT XR® safely and effectively. See full prescribing information for QUILLIVANT XR®.

QUILLIVANT XR® (methylphenidate hydrochloride) for extended-release oral suspension, CII

Initial U.S. Approval: 1955

### WARNING: ABUSE, MISUSE, AND ADDICTION

See full prescribing information for complete boxed warning.

QUILLIVANT XR has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including QUILLIVANT XR, can result in overdose and death (5.1, 9.2, 10):

- Before prescribing QUILLIVANT XR, assess each patient's risk for abuse, misuse, and addiction.
- Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug.
- Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

### RECENT MAJOR CHANGES

Boxed Warning	10/2023
Dosage and Administration (2.1, 2.2, 2.5)	10/2023
Warnings and Precautions (5.1, 5.2, 5.8, 5.9, 5.10)	10/2023

### INDICATIONS AND USAGE

QUILLIVANT XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). (1)

### DOSAGE AND ADMINISTRATION

- Before administering the dose, vigorously shake bottle for at least 10 seconds. (2.2)
- May be taken with or without food. (2.3)
- For patients 6 years and above, recommended starting dose is 20 mg given orally once daily in the morning. Dosage may be increased weekly in increments of 10 mg to 20 mg per day. Daily dosage above 60 mg is not recommended. (2.2)
- Reconstitution instructions for the pharmacist: Tap bottle until powder flows freely. Remove bottle cap, add specified amount of water for reconstitution. Insert bottle adapter into neck of bottle. Replace bottle cap. Shake with vigorous back and forth motion for at least 10 seconds to prepare suspension. (2.6)

### DOSAGE FORMS AND STRENGTHS

Extended-release oral suspension (after reconstitution with water): 25 mg per 5 mL (5 mg per mL). (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

- *Risks to Patients with Serious Cardiac Disease:* Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac disease. (5.2)
- *Increased Blood Pressure and Heart Rate:* Monitor blood pressure and pulse. (5.3)
- *Psychiatric Adverse Reactions:* Prior to initiating QUILLIVANT XR, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing QUILLIVANT XR. (5.4)
- *Priapism:* If abnormally sustained or frequent and painful erections occur, patients should seek immediate medical attention. (5.5)
- *Peripheral Vasculopathy, including Raynaud's Phenomenon:* Careful observation for digital changes is necessary during QUILLIVANT XR treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy. (5.6)
- *Long-Term Suppression of Growth in Pediatric Patients:* Closely monitor growth (height and weight) in pediatric patients. Pediatric patients not growing or gaining height or weight as expected may need to have their treatment interrupted. (5.7)
- *Acute Angle Closure Glaucoma:* QUILLIVANT XR -treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist. (5.8)
- *Increased Intraocular Pressure (IOP) and Glaucoma:* Prescribe QUILLIVANT XR to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Closely monitor patients with a history of increased IOP or open angle glaucoma. (5.9)
- *Motor and Verbal Tics, and Worsening of Tourette's Syndrome:* Before initiating QUILLIVANT XR, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome. Discontinue treatment if clinically appropriate. (5.10)

### ADVERSE REACTIONS

Based on accumulated data from other methylphenidate products, the most common ( $\geq 5\%$  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 Tris Pharma, Inc. at 732-940-0358 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Antihypertensive Drugs: Monitor blood pressure. Adjust dosage of antihypertensive drug as needed. (7)

See 17 for PATIENT COUNSELING INFORMATION and [Medication Guide](#).

Revised: 10/2023

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## FULL PRESCRIBING INFORMATION

### WARNING: ABUSE, MISUSE, AND ADDICTION

QUILLIVANT XR has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including QUILLIVANT XR, can result in overdose and death [see *Overdosage (10)*], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing QUILLIVANT XR, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug. Throughout QUILLIVANT XR treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction [see *Warnings and Precautions (5.1)*, *Drug Abuse and Dependence (9.2)*].

## 1 INDICATIONS AND USAGE

QUILLIVANT XR 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 patients with QUILLIVANT XR, 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)*].
- the family history and clinically evaluate patients for motor or verbal tics or Tourette's syndrome before initiating QUILLIVANT XR [see *Warnings and Precautions (5.10)*].

### 2.2 Recommended Dosage

Before administering the dose, **VIGOROUSLY SHAKE** the bottle of QUILLIVANT XR for at least 10 seconds, to ensure that the proper dose is administered.

The recommended starting dose of QUILLIVANT XR for patients 6 years and above is 20 mg once daily in the morning. The dose may be titrated weekly in increments of 10 mg to 20 mg. Daily doses above 60 mg have not been studied and are not recommended. As with any CNS stimulant, during titration of QUILLIVANT XR, the prescribed dose should be adjusted, if necessary, until a well-tolerated, therapeutic dose is achieved.

Patients should be advised to avoid alcohol while taking QUILLIVANT XR [see *Clinical Pharmacology (12.3)*].

## 2.3 Administration Instructions

QUILLIVANT XR 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 QUILLIVANT XR 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), *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. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

## 2.6 Reconstitution Instructions for the Pharmacist

QUILLIVANT XR is supplied as a powder for oral suspension which must be reconstituted with water prior to dispensing. Preparation instructions: Tap bottle until powder flows freely. Remove bottle cap, and add specified amount of water to the bottle (see Table 1 below). Fully insert bottle adapter into neck of bottle [see *Instructions for Use, Figures F and G*]. Replace bottle cap. Shake with vigorous back and forth motion for at least 10 seconds to prepare suspension.

**Table 1: Product Reconstitution Instructions**

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

Store reconstituted QUILLIVANT XR at 25°C (77°F); excursions permitted from 15° to 30°C (59° to 86°F). Dispense in original packaging (bottle in carton) with bottle adapter inserted and with enclosed oral dosing dispenser. QUILLIVANT XR is stable for up to 4 months after reconstitution.

### **3 DOSAGE FORMS AND STRENGTHS**

Extended-release oral suspension (after reconstitution with water): 25 mg per 5 mL (5 mg per mL).

### **4 CONTRAINDICATIONS**

#### **4.1 Hypersensitivity to Methylphenidate or other Components of QUILLIVANT XR**

QUILLIVANT XR is contraindicated in patients known to be hypersensitive to methylphenidate, or other components of QUILLIVANT XR. 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**

QUILLIVANT XR is contraindicated during 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 Abuse, Misuse, and Addiction**

QUILLIVANT XR has a high potential for abuse and misuse. The use of QUILLIVANT XR exposes individuals to the risks of abuse and misuse, which can lead to the development of a substance use disorder, including addiction. QUILLIVANT XR can be diverted for non-medical use into illicit channels or distribution [see *Drug Abuse and Dependence* (9.2)]. Misuse and abuse of CNS stimulants, including QUILLIVANT XR, can result in overdose and death [see *Overdosage* (10)], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing QUILLIVANT XR, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks and proper disposal of any unused drug. Advise patients to store QUILLIVANT XR in a safe place, preferably locked, and instruct patients to not give QUILLIVANT XR to anyone else. Throughout QUILLIVANT XR treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

#### **5.2 Risks to Patients with Serious Cardiac Disease**

Sudden death has occurred in patients with structural cardiac abnormalities or other serious cardiac disease who were treated with CNS stimulants at the recommended ADHD dosage.

Avoid QUILLIVANT XR use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac disease.

### **5.3 Increased Blood Pressure and Heart Rate**

CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mm Hg) and heart rate (mean increase approximately 3 to 6 bpm). Some patients may have larger increases.

Monitor all QUILLIVANT XR-treated 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 QUILLIVANT XR 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 the recommended dosage, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. 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 % of placebo-treated patients. If such symptoms occur, consider discontinuing QUILLIVANT XR.

### **5.5 Priapism**

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate use in both adults and pediatric male patients. Although priapism was not reported with methylphenidate initiation, it developed after some time on methylphenidate, often subsequent to an increase in dosage. Priapism also occurred during a methylphenidate withdrawal (drug holidays or during discontinuation).

QUILLIVANT XR-treated 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 QUILLIVANT XR, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, sequelae have included digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were

observed in post-marketing reports and at the therapeutic dosage of CNS stimulants in all age groups throughout the course of treatment. Signs and symptoms generally improved after dosage reduction or discontinuation of the CNS stimulant.

Careful observation of digital changes is necessary during QUILLIVANT XR treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for QUILLIVANT XR-treated patients who develop signs or symptoms of peripheral vasculopathy.

### **5.7 Long-Term Suppression of Growth in Pediatric Patients**

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 pediatric patients who received methylphenidate for 7 days per week throughout the year had 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 development period.

Closely monitor growth (weight and height) in QUILLIVANT XR-treated pediatric patients. Pediatric patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

### **5.8 Acute Angle Closure Glaucoma**

There have been reports of angle closure glaucoma associated with methylphenidate treatment.

Although the mechanism is not clear, QUILLIVANT XR -treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist.

### **5.9 Increased Intraocular Pressure and Glaucoma**

There have been reports of an elevation of intraocular pressure (IOP) associated with methylphenidate treatment [*see Adverse Reactions (6.2)*].

Prescribe QUILLIVANT XR to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Closely monitor QUILLIVANT XR -treated patients with a history of abnormally increased IOP or open angle glaucoma.

### **5.10 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 [*see Adverse Reactions (6.2)*].

Before initiating QUILLIVANT XR, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor QUILLIVANT XR -treated patients for the emergence or worsening of tics or Tourette's syndrome, and discontinue treatment if clinically appropriate.



## 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 QUILLIVANT XR [see *Contraindications (4)*]
- Hypertensive Crisis When Used Concomitantly with Monoamine Oxidase Inhibitors [see *Contraindications (4)*, *Drug Interactions (7.1)*]
- Abuse, Misuse, and Addiction [see *Boxed Warning, Warnings and Precautions (5.1)*, *Drug Abuse and Dependence (9.2, 9.3)*]
- Risks to Patients with Serious Cardiac Disease [see *Warnings and Precautions (5.2)*]
- Increased Blood Pressure and Heart Rate [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 in Pediatric Patients [see *Warnings and Precautions (5.7)*]
- Acute Angle Closure Glaucoma [see *Warnings and Precautions (5.8)*]
- Increased Intraocular Pressure and Glaucoma [see *Warnings and Precautions (5.9)*]
- Motor and Verbal Tics, and Worsening of Tourette’s Syndrome [see *Warnings and Precautions (5.10)*]

### 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.

*Adverse Reactions in Studies with Other Methylphenidate Products in Children, Adolescents, and Adults with ADHD*

Commonly reported ( $\geq 2\%$  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.

*Adverse Reactions in Studies with QUILLIVANT XR in Children and Adolescents with ADHD*

There is limited experience with QUILLIVANT XR in controlled trials. Based on this limited experience, the adverse reaction profile of QUILLIVANT XR appears similar to other methylphenidate extended-release products. The most common ( $\geq 2\%$  in the QUILLIVANT XR

group and greater than placebo) adverse reactions reported in the Phase 3 controlled study conducted in 45 ADHD patients (ages 6 to 12 years) were affect lability, excoriation, initial insomnia, tic, decreased appetite, vomiting, motion sickness, eye pain, and rash.

**Table 2: Common Adverse Reactions occurring in  $\geq 2\%$  of subjects on QUILLIVANT XR and greater than placebo during the controlled cross-over phase**

Adverse reaction	QUILLIVANT XR N= 45	Placebo N= 45
Affect lability	9%	2%
Excoriation	4%	0
Initial Insomnia	2%	0
Tic	2%	0
Decreased appetite	2%	0
Vomiting	2%	0
Motion sickness	2%	0
Eye pain	2%	0
Rash	2%	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, Extra systole, Supraventricular tachycardia, Ventricular extra systole

*Eye Disorders:* Diplopia, Increased intraocular pressure, 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, Motor and Verbal Tics

*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**

#### **MAOI Inhibitors**

Do not administer QUILLIVANT XR 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.

#### **Antihypertensive Drugs**

QUILLIVANT XR may decrease the effectiveness of drugs used to treat hypertension. Monitor blood pressure and adjust the dosage of the hypertensive drug as needed [*see Warnings and Precautions (5.3)*].

#### **Halogenated Anesthetics**

Concomitant use of halogenated anesthetics and QUILLIVANT XR may increase the risk of sudden blood pressure and heart rate increase during surgery. Monitor blood pressure and avoid use of QUILLIVANT XR in patients being treated with anesthetics on the day of surgery.

#### **Risperidone**

Combined use of methylphenidate with risperidone when there is a change, whether an increase or decrease, in dosage of either or both medications, may increase the risk of extrapyramidal symptoms (EPS). Monitor for signs of EPS.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### *Pregnancy Exposure Registry*

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visiting online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/othermedications/>.

#### 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% to 4% and 15% to 20%, respectively.

#### Clinical Considerations

##### *Fetal/Neonatal adverse reactions*

CNS stimulant medications, such as QUILLIVANT XR, 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<sup>2</sup> basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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 QUILLIVANT XR and any potential adverse effects on the breastfed infant from QUILLIVANT XR 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 QUILLIVANT XR have been established in pediatric patients ages 6 to 17 years. Use of QUILLIVANT XR in pediatric patients 6 to 12 years of age is supported by one adequate and well-controlled study [*see Clinical Studies (14)*]. Use in 12 to 17 year olds is supported by the adequate and well-controlled studies of QUILLIVANT XR in younger pediatric patients and additional pharmacokinetic data in adolescents, along with safety information from other methylphenidate-containing products. The safety and effectiveness of QUILLIVANT XR in pediatric patients less than 6 years have not been established.

The long-term efficacy of methylphenidate in pediatric patients has not been established.

### Long Term Suppression of Growth

Growth should be monitored during treatment with CNS stimulants, including QUILLIVANT XR. 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<sup>2</sup> 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 to 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<sup>2</sup> 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<sup>2</sup> basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m<sup>2</sup> basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

## **8.5 Geriatric Use**

QUILLIVANT XR has not been studied in patients over the age of 65 years.

## **9 DRUG ABUSE AND DEPENDENCE**

### **9.1 Controlled Substance**

QUILLIVANT XR contains methylphenidate, a Schedule II controlled substance.

### **9.2 Abuse**

QUILLIVANT XR has a high potential for abuse and misuse which can lead to the development of a substance use disorder, including addiction [*see Warnings and Precautions (5.1)*].

QUILLIVANT XR can be diverted for non-medical use into illicit channels or distribution.

Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of methylphenidate may cause increased heart rate, respiratory rate, or blood pressure; sweating; dilated pupils; hyperactivity; restlessness; insomnia; decreased appetite; loss of coordination; tremors; flushed skin; vomiting; and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including QUILLIVANT XR, can result in overdose and death [*see Overdosage (10)*], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

### **9.3 Dependence**

#### Physical Dependence

QUILLIVANT XR may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal signs and symptoms after abrupt discontinuation or dose reduction following prolonged use of CNS stimulants including QUILLIVANT XR include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

#### Tolerance

QUILLIVANT XR may produce tolerance. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

## 10 OVERDOSAGE

### Clinical Effects of Overdose

Overdose of CNS stimulants is characterized by the following sympathomimetic effects:

- Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden cardiac death. Takotsubo cardiomyopathy may develop.
- CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin syndrome, seizures, cerebral vascular accidents, and coma may occur.
- Life-threatening hyperthermia (temperatures greater than 104°F) and rhabdomyolysis may develop.

### Overdose Management

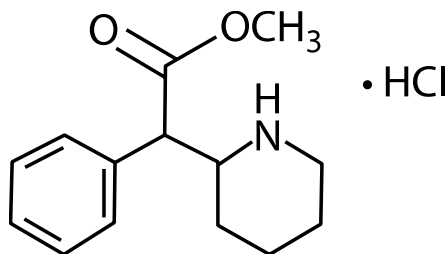
Consider the possibility of multiple drug ingestion. The pharmacokinetic profile of QUILLIVANT XR should be considered when treating patients with overdose. Because methylphenidate has a large volume of distribution and is rapidly metabolized, dialysis is not useful. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

## 11 DESCRIPTION

QUILLIVANT XR is a powder that, after reconstitution with water, forms an extended-release oral suspension formulation of methylphenidate intended for once daily oral administration. QUILLIVANT XR contains approximately 20% immediate-release and 80% extended-release methylphenidate. After reconstitution, QUILLIVANT XR is available in a 25 mg per 5 mL (5 mg per mL) extended-release oral suspension.

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

**Figure 1: Methylphenidate HCl structure**



C<sub>14</sub>H<sub>19</sub>NO<sub>2</sub>•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.

QUILLIVANT XR also contains the following inactive ingredients: sodium polystyrene sulfonate, povidone, triacetin, polyvinyl acetate, sucrose, anhydrous trisodium citrate, anhydrous citric acid, sodium benzoate, sucralose, poloxamer 188, corn starch, xanthan gum, talc, banana flavor, and silicon dioxide.

## **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 increases the release of these monoamines into the extraneuronal space.

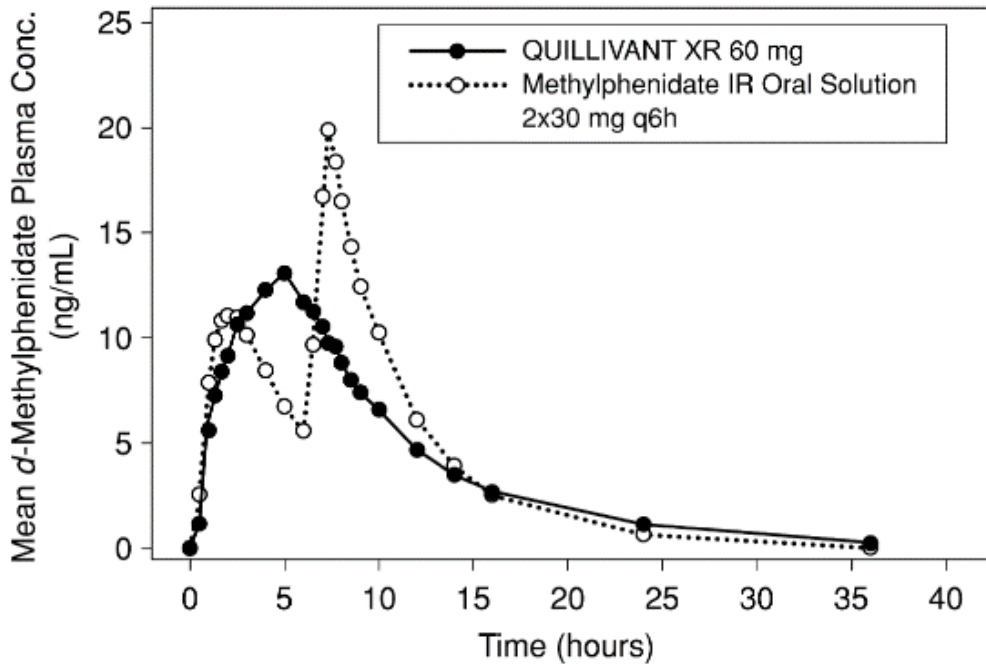
### **12.3 Pharmacokinetics**

#### *Absorption*

Following a single, 60 mg oral dose of QUILLIVANT XR in 28 healthy adult subjects in a crossover study under fasting conditions, *d*-methylphenidate (*d*-MPH) mean ( $\pm$  SD) peak plasma concentrations of 13.6 ( $\pm$  5.8) ng/mL occurred at a median time of 5 hours after dosing (Figure 2). The relative bioavailability of QUILLIVANT XR compared to Methylphenidate IR oral solution (2x30 mg, q6h) is 95%.



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



The single dose pharmacokinetics of *d*-MPH under fed conditions are summarized (Table 3) from studies in children and adolescents with ADHD, and healthy adults following an oral dose of 60 mg QUILLIVANT XR.

**Table 3: *d*-MPH PK Parameters (mean  $\pm$ SD) after 60 mg oral dosing of QUILLIVANT XR\***

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

\* Breakfast was given 30 min prior to drug administration

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

‡ data presented as median (range)

### Food Effects

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

### Elimination

Following a single 60 mg oral dose of QUILLIVANT XR in 28 healthy adult subjects under fasting conditions, the mean plasma terminal elimination half-life of *d*-methylphenidate was 5.6 ( $\pm$  0.8) hours.

### Metabolism

In humans, methylphenidate is metabolized primarily via deesterification 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

An *in vitro* study was conducted to explore the effect of alcohol on the release characteristics of methylphenidate from QUILLIVANT XR Oral Suspension. At alcohol concentrations of 5% and 10%, there was no effect of alcohol on the release characteristics of methylphenidate. At 20% alcohol concentration, there was on average a 20% increase in drug exposure [*see Dosage and Administration (2.2)*].

### Specific Populations

#### Sex

There is insufficient experience with the use of QUILLIVANT XR to detect gender variations in pharmacokinetics.

#### Race

There is insufficient experience with the use of QUILLIVANT XR to detect ethnic variations in pharmacokinetics.

#### Age

The pharmacokinetics of methylphenidate after QUILLIVANT XR administration were studied in pediatric patients with ADHD between 9 and 15 years of age. After a single oral dose of 60 mg QUILLIVANT XR, plasma concentrations of methylphenidate in children (9 to 12 years old; n=3) were approximately twice the concentrations observed in adults. The plasma concentrations in adolescent patients (13 to 15 years old; n=4) were similar to those in adults.

#### Renal Impairment

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

#### Hepatic Impairment

There is no experience with the use of QUILLIVANT XR 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> basis.

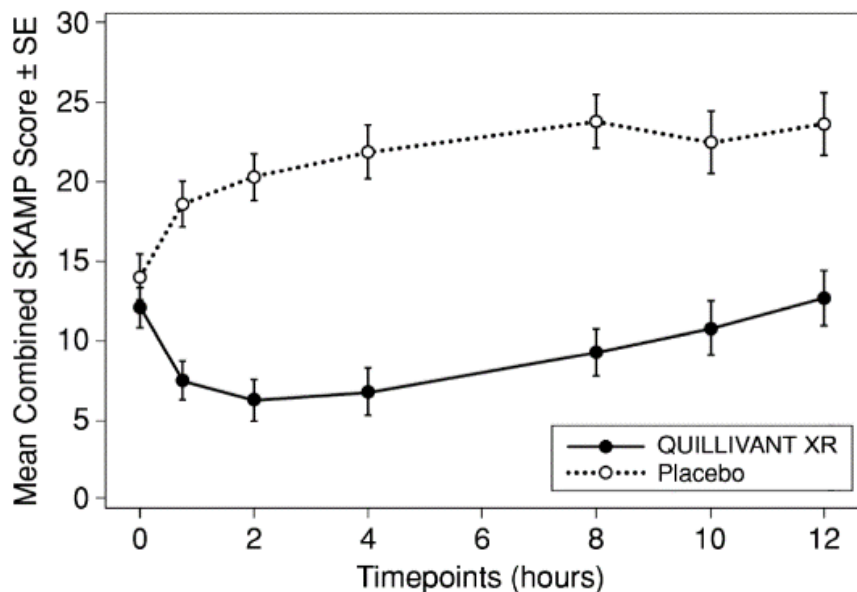
## **14 CLINICAL STUDIES**

The efficacy of QUILLIVANT XR was evaluated in a laboratory classroom study conducted in 45 pediatric patients (ages 6 to 12 years) with ADHD. Patients in the trial met Diagnostic and Statistical Manual of Mental Diseases, 4th edition (DSM-IV®) criteria for ADHD. The study began with an open-label dose optimization period (4 to 6 weeks) with an initial QUILLIVANT XR dose of 20 mg once daily in the morning. The dose could be titrated weekly in increments of

10 or 20 mg until a therapeutic dose or the maximum dose of 60 mg/day was reached. At the end of the dose optimization period, approximately 5% of subjects were receiving 20 mg/day; 39%, 30 mg/day; 31%, 40 mg/day; 10%, 50 mg/day; and 15%, 60 mg/day. Subjects then entered a 2-week randomized, double-blind, crossover treatment with the individually optimized dose of QUILLIVANT XR or placebo. At the end of each week, school teachers and raters evaluated the attention and behavior of the subjects in a laboratory classroom using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale. The primary efficacy endpoint was the SKAMP-Combined score at 4 hours post-dosing. The key secondary efficacy endpoints were the SKAMP-Combined scores at 0.75, 2, 8, 10, and 12 hours post-dosing.

Results from the first double-blind, placebo-controlled week of the study are summarized in Figure 3. SKAMP-Combined scores were statistically significantly lower (improved) at all time points (0.75, 2, 4, 8, 10, 12 hours) post-dosing with QUILLIVANT XR compared to placebo.

**Figure 3: Absolute SKAMP-Combined Score after treatment with QUILLIVANT XR or Placebo during Period 1.**



## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

QUILLIVANT XR is supplied as powder that, after reconstitution with water, forms an extended-release oral suspension. The product is supplied in a carton. Each carton also contains one bottle, one oral dosing dispenser, and one bottle adapter.

The product must be reconstituted only by the pharmacist and not by the patient or caregiver. After reconstitution, the product is a light beige to tan viscous suspension containing 25 mg per 5 mL (5 mg per mL) of methylphenidate hydrochloride.

Bottles of 300 mg powder (to prepare 60 mL suspension) NDC 24478-321-02

Bottles of 600 mg powder (to prepare 120 mL suspension) NDC 24478-322-04

Bottles of 750 mg powder (to prepare 150 mL suspension) NDC 24478-323-05

Bottles of 900 mg powder (to prepare 180 mL suspension) NDC 24478-324-06

## 16.2 Storage and Handling

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

Dispense in original container.

## 17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling ([Medication Guide](#) and [Instructions for Use](#)).

### Abuse, Misuse, and Addiction

Educate patients and their families about the risks of abuse, misuse, and addiction of QUILLIVANT XR, which can lead to overdose and death, and proper disposal of any unused drug [see *Warnings and Precautions (5.1)*, *Drug Abuse and Dependence (9.2)*, *Overdosage (10)*]. Advise patients to store QUILLIVANT XR in a safe place, preferably locked, and instruct patients to not give QUILLIVANT XR to anyone else.

### Instructions for Using the Enclosed Oral Dosing Dispenser

Provide the following instructions on administration to the patient or caregiver:

- The pharmacist should provide this medicine in its original packaging (bottle within carton) with the bottle adapter fully inserted and the accompanying oral dosing dispenser. Use only with the oral dosing dispenser provided with this product.
- Check and make sure that the QUILLIVANT XR bottle contains liquid medicine. If QUILLIVANT XR is in powder form, do not use it. Return it to your pharmacist.
- **VIGOROUSLY SHAKE** the bottle of QUILLIVANT XR for at least 10 seconds before each dose, to ensure that the proper dose is administered.
- Remove the bottle cap. Confirm that the bottle adapter has been inserted into top of the bottle.
- Insert the tip of the oral dosing dispenser provided with this product into the bottle adapter.
- Turn bottle upside down and withdraw prescribed amount of QUILLIVANT XR into the oral dosing dispenser.
- Remove filled oral dosing dispenser from bottle and dispense QUILLIVANT XR directly into mouth.
- Replace bottle cap and store bottle as directed.

- Wash oral dosing dispenser after each use (components are dishwasher-safe).

#### Risks to Patients with Serious Cardiac Disease

Advise patients that there are potential risks to patients with serious cardiac disease, including sudden death with QUILLIVANT XR 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)*].

#### Increased Blood Pressure and Heart Rate

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

#### Psychiatric Adverse Reactions

Advise patients that QUILLIVANT XR, 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 QUILLIVANT XR 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 QUILLIVANT XR.**
- Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients [see *Warnings and Precautions (5.6)*].

#### Long-Term Suppression of Growth in Pediatric Patients

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

#### Increased Intraocular Pressure (IOP) and Glaucoma

Advise patients that IOP and glaucoma may occur during treatment with QUILLIVANT XR [see *Warnings and Precautions (5.9)*].

#### Motor and Verbal Tics, and Worsening of Tourette's Syndrome

Advise patients that motor and verbal tics and worsening of Tourette's Syndrome may occur during treatment with QUILLIVANT XR. Instruct patients to notify their healthcare provider if

emergence of new tics or worsening of tics or Tourette's syndrome occurs [see *Warnings and Precautions (5.10)*].

#### Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to QUILLIVANT XR during pregnancy [see *Use in Specific Populations (8.1)*].

#### Alcohol Effect

Patients should be advised to avoid alcohol while taking QUILLIVANT XR Oral Suspension. Consumption of alcohol while taking QUILLIVANT XR may result in a more rapid release of the dose of methylphenidate [see *Clinical Pharmacology (12.3)*].

This product's label may have been updated. For current full prescribing information, please visit [www.trispharma.com](http://www.trispharma.com)

Distributed by:

**NextWave Pharmaceuticals, Inc**

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Manufactured by:

**Tris Pharma, Inc.**

Monmouth Junction, NJ 08852

LB8529

Rev.02

## Medication Guide

### QUILLIVANT XR® (kwil-ə-vant\ (methylphenidate hydrochloride) for extended-release oral suspension CII

#### What is the most important information I should know about QUILLIVANT XR?

#### QUILLIVANT XR may cause serious side effects, including:

- **Abuse, misuse, and addiction.** QUILLIVANT XR has a high chance for abuse and misuse and may lead to substance use problems, including addiction. Misuse and abuse of QUILLIVANT XR, other methylphenidate containing medicines, and amphetamine containing medicines, can lead to overdose and death. The risk of overdose and death is increased with higher doses of QUILLIVANT XR or when it is used in ways that are not approved, such as snorting or injection.
  - Your healthcare provider should check you or your child’s risk for abuse, misuse, and addiction before starting treatment with QUILLIVANT XR and will monitor you or your child during treatment.
  - QUILLIVANT XR may lead to physical dependence after prolonged use, even if taken as directed by your healthcare provider.
  - Do not give QUILLIVANT XR to anyone else. See “**What is QUILLIVANT XR?**” for more information.
  - Keep QUILLIVANT XR in a safe place and properly dispose of any unused medicine. See “**How should I store QUILLIVANT XR?**” for more information.
  - Tell your healthcare provider if you or your child have ever abused or been dependent on alcohol, prescription medicines, or street drugs.

**Risks for people with serious heart disease.** Sudden death has happened in people who have heart defects or other serious heart disease.

- Your healthcare provider should check you or your child carefully for heart problems before starting treatment with QUILLIVANT XR.

Tell your health care provider if you or your child have any heart problems, heart disease, or heart defects.

**Call your healthcare provider or go to the nearest hospital emergency room right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking QUILLIVANT XR.**



- **Increased blood pressure and heart rate.**

Your health care provider should check your or your child's blood pressure and heart rate regularly during treatment with QUILLIVANT XR.

- **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 QUILLIVANT XR, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.**

### **What is QUILLIVANT XR?**

QUILLIVANT XR is a central nervous system stimulant prescription medicine.

**QUILLIVANT XR is a liquid medicine** that you take by mouth.

**It is used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).**

QUILLIVANT XR may help increase attention and decrease impulsiveness and hyperactivity in people with ADHD.

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

**QUILLIVANT XR is a federally controlled substance (CII) because it contains methylphenidate that can be a target for people who abuse prescription medicines or street drugs.** Keep QUILLIVANT XR in a safe place to protect it from theft. Never give your QUILLIVANT XR to anyone else, because it may cause death or harm them. Selling or giving away QUILLIVANT XR may harm others and is against the law.

### **Do not take QUILLIVANT XR if you or your child:**

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

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

- heart problems, heart disease, heart defects, or high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- circulation problems in fingers and toes
- have eye problems, including increased pressure in your eye, glaucoma, or problems with your close-up vision (farsightedness)
- have or had repeated movements or sounds (tics) or Tourette's syndrome, or have a family history of tics or Tourette's syndrome
- if you are pregnant or plan to become pregnant. It is not known if QUILLIVANT XR will harm your unborn baby. Talk to your health care provider if you are pregnant or plan to become pregnant.
  - There is a pregnancy registry for females who are exposed to ADHD medications during pregnancy. The purpose of the registry is to collect information about the health of females exposed to QUILLIVANT XR and their baby. If you or your child becomes pregnant during treatment with QUILLIVANT XR, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visit <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/othermedications/>.
- if you are breastfeeding or plan to breast feed. QUILLIVANT XR passes into your breast milk. You and your healthcare provider should decide if you will take QUILLIVANT XR or breast feed.

**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.** QUILLIVANT XR 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 QUILLIVANT XR.

Your health care provider will decide whether QUILLIVANT XR can be taken with other medicines.

**Especially tell your 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 QUILLIVANT XR without talking to your health care provider first.**

### **How should QUILLIVANT XR be taken?**

- **Read the step-by-step instructions for using QUILLIVANT XR extended-release suspension at the end of this Medication Guide.**
- Take QUILLIVANT XR 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.
- QUILLIVANT XR should be used with the oral dosing dispenser provided with the product. If the oral dosing dispenser is missing or not provided, please contact your pharmacist for a replacement.
- Check and make sure that the QUILLIVANT XR bottle contains liquid medicine. If QUILLIVANT XR is in powder form, do not use it. Return it to your pharmacist.
- Check and make sure that the bottle adapter was fully inserted into the bottle by the pharmacist. If the bottle adapter is not fully inserted, insert the adapter into the bottle.
- Take QUILLIVANT XR 1 time each day in the morning. QUILLIVANT XR is an extended-release suspension. It releases medicine into your body throughout the day.
- QUILLIVANT XR can be taken with or without food. Taking QUILLIVANT XR with food may shorten the time it takes for the medicine to start working.
- Your health care provider may do regular checks of the blood, heart, and blood pressure while taking QUILLIVANT XR.
- Children should have their height and weight checked often while taking QUILLIVANT XR. QUILLIVANT XR treatment may be stopped if a problem is found during these check-ups.
- If a dose is missed, you or your child should talk to your health care provider about dosing.

If you or your child take too much QUILLIVANT XR, call your healthcare provider or Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

### **What should I avoid while taking QUILLIVANT XR?**

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

### **What are the possible side effects of QUILLIVANT XR?**

**QUILLIVANT XR may cause serious side effects, including:**

- See “**What is the most important information I should know about QUILLIVANT XR?**” 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.**

- **Circulation problems in fingers and toes (peripheral vasculopathy, including Raynaud’s phenomenon):**

**Signs and symptoms may include:**

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

Tell your healthcare provider if you or your child have numbness, pain, skin color change, or sensitivity to temperature in your fingers or toes, or if you or your child have any signs of unexplained wounds appearing on fingers or toes during treatment with QUILLIVANT XR.

- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with QUILLIVANT XR. QUILLIVANT XR treatment may be stopped if your child is not gaining weight or height.
- **Eye problems (increased pressure in the eye and glaucoma).** Call your healthcare provider right away if you or your child develop changes in your vision or eye pain, swelling, or redness.
- **New or worsening tics or worsening Tourette’s syndrome.** Tell your healthcare provider if you or your child get any new or worsening tics or worsening Tourette’s syndrome during treatment with QUILLIVANT XR.

**The most common side effects of QUILLIVANT XR 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 QUILLIVANT XR.

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

#### **How should I store QUILLIVANT XR?**

- Store QUILLIVANT XR at 59°F to 86°F (15°C to 30°C).
- Store QUILLIVANT XR in a safe place, like a locked cabinet.
- Dispose of remaining, unused, or expired QUILLIVANT XR by a medicine take-back program at a U.S. Drug Enforcement Administration (DEA) authorized collection site. If no take-back program or DEA authorized collector is available, mix QUILLIVANT XR with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away QUILLIVANT XR in the household trash. Visit <http://www.fda.gov/drugdisposal> for additional information on disposal of unused medicines.
- **Keep QUILLIVANT XR and all medicines out of the reach of children.**

#### **General information about the safe and effective use of QUILLIVANT XR**

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

You can ask your pharmacist or healthcare provider for information about QUILLIVANT XR that is written for healthcare professionals.

#### **What are the ingredients in QUILLIVANT XR?**

**Active Ingredient:** methylphenidate hydrochloride

**Inactive Ingredients:** sodium polystyrene sulfonate, povidone, triacetin, polyvinyl acetate, sucrose, anhydrous trisodium citrate, anhydrous citric acid, sodium benzoate, sucralose, poloxamer 188, corn starch, xanthan gum, talc, banana flavor, and silicon dioxide.

Distributed by:

**NextWave Pharmaceuticals, Inc**

A subsidiary of Tris Pharma, Inc., Monmouth Junction, NJ 08852

Manufactured by:

**Tris Pharma, Inc.**

Monmouth Junction, NJ 08852

LB8529

For more information, go to [www.quillivantxr.com](http://www.quillivantxr.com) or call (732)-940-0358.

This product's label may have been updated. For current full prescribing information, please visit [www.trispharma.com](http://www.trispharma.com).

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

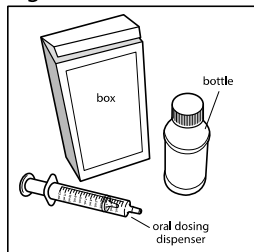
Revised: 10/2023

**Instructions for Use**  
**QUILLIVANT XR® (kwil-ə-vant)**  
**(methylphenidate hydrochloride)**  
**for extended-release oral suspension CII**

Read this Instructions for Use before using QUILLIVANT XR and each time you get a refill. There may be new information. This leaflet does not take the place of talking with the health care provider about your or your child's medical condition or treatment.

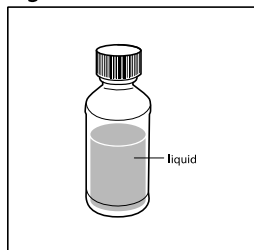
**Step 1.** Remove the QUILLIVANT XR bottle and oral dosing dispenser from the box (See **Figure A**). If the oral dosing dispenser is missing or not provided, please contact your pharmacist for a replacement.

Figure A



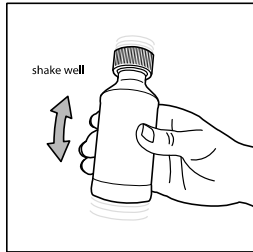
**Step 2.** Check and make sure that the QUILLIVANT XR bottle contains liquid medicine (See **Figure B**). If QUILLIVANT XR is still in powder form, **do not use it**. Return it to your pharmacist.

Figure B



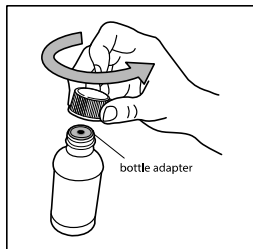
**Step 3. Shake the bottle well** (up and down) for at least 10 seconds before each use (See **Figure C**).

Figure C



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

Figure D



**Step 4 (continued).** If bottle adapter (**See Figure E**) has not been inserted by the pharmacist into the bottle, insert adapter into the bottle as shown (**See Figure E and Figure F**).

Figure E

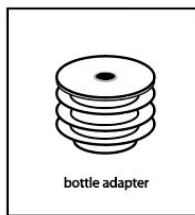
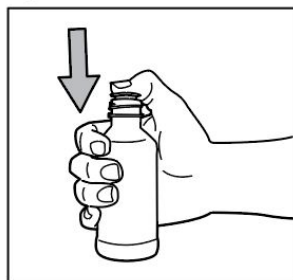


Figure F

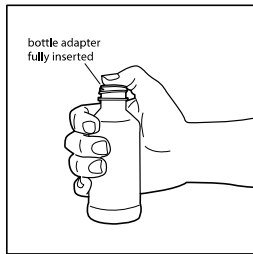


After the bottle adapter has been fully inserted into the bottle (**See Figure G**), it should not be removed. If the bottle adapter has not been inserted and is missing from the box, contact your pharmacist.

The bottle adapter must be fully inserted and should be even with the mouth of the bottle and must remain in place to allow the child resistant cap to work the right way.

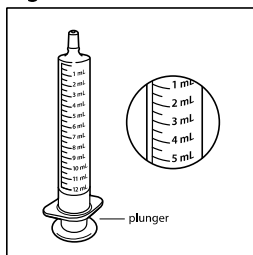


Figure G



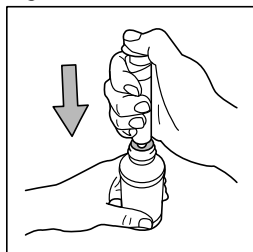
**Step 5.** Check the QUILLIVANT XR dose in milliliters (mL) as prescribed by your health care provider. Locate this number on the oral dosing dispenser (See **Figure H**).

Figure H



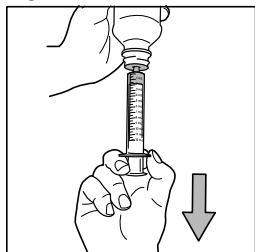
**Step 6.** Insert tip of the oral dosing dispenser into the upright bottle and push the plunger all the way down (See **Figure I**).

Figure I



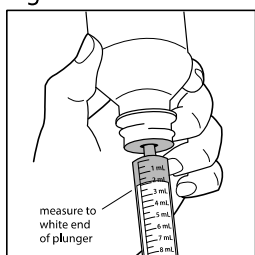
**Step 7.** With the oral dosing dispenser in place, turn the bottle upside down. Pull the plunger to the number of mL you need (the amount of liquid medicine in **Step 5** – See **Figure J**).

Figure J



**Step 7 (continued).** Measure the number of mL of medicine from the white end of the plunger (See Figure K).

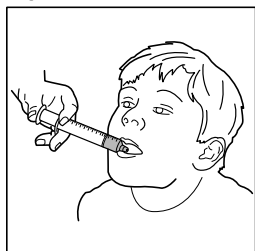
Figure K



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

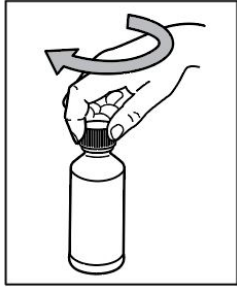
**Step 9.** Slowly squirt QUILLIVANT XR directly into your or your child's mouth (See Figure L).

Figure L



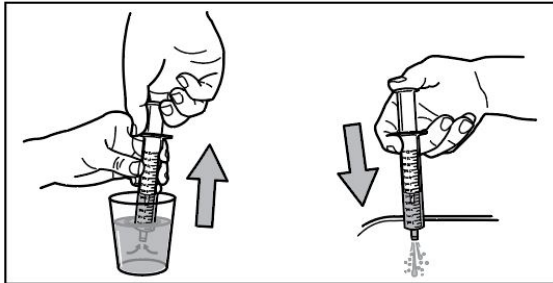
**Step 10.** Cap the bottle tightly. Store the bottle upright at 59°F to 86°F (15°C to 30°C) (See Figure M).

Figure M



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

Figure N



These Instructions for Use have been approved by the U.S. Food and Drug Administration. This product's label may have been updated. For current full prescribing information, please visit [www.trispharma.com](http://www.trispharma.com).

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LB8529 Rev. 01 06/2021

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use QUILLICHEW ER<sup>®</sup> safely and effectively. See full prescribing information for QUILLICHEW ER<sup>®</sup>.

QUILLICHEW ER<sup>®</sup> (methylphenidate hydrochloride) extended-release chewable tablets, for oral use, CII

Initial U.S. Approval: 1955

### WARNING: ABUSE, MISUSE, AND ADDICTION

See full prescribing information for complete boxed warning.

**QUILLICHEW ER has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including QUILLICHEW ER, can result in overdose and death (5.1, 9.2, 10):**

- Before prescribing QUILLICHEW ER, assess each patient's risk for abuse, misuse, and addiction.
- Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug.
- Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

### RECENT MAJOR CHANGES

Boxed Warning	10/2023
Dosage and Administration (2.1, 2.2, 2.5)	10/2023
Warnings and Precautions (5.1, 5.2, 5.9, 5.10, 5.11)	10/2023

### 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, 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

- *Risks to Patients with Serious Cardiac Disease:* Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac disease. (5.2)
- *Increased Blood Pressure and Heart Rate:* Monitor blood pressure and pulse. (5.3)
- *Psychiatric Adverse Reactions:* Prior to initiating QuilliChew ER, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing QuilliChew ER. (5.4)
- *Priapism:* If abnormally sustained or frequent and painful erections occur, patients should seek immediate medical attention. (5.5)
- *Peripheral Vasculopathy, including Raynaud's Phenomenon:* Careful observation for digital changes is necessary during QuilliChew ER treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy. (5.6)

- *Long-Term Suppression of Growth in Pediatric Patients:* Closely monitor growth (height and weight) in pediatric patients. Pediatric patients not growing or gaining height or weight as expected may need to have their treatment interrupted. (5.7)
- *Risks in Phenylketonurics:* QuilliChew ER extended-release chewable tablets contain phenylalanine, a component of aspartame. (5.8)
- *Acute Angle Closure Glaucoma:* QuilliChew ER -treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist. (5.9)
- *Increased Intraocular Pressure (IOP) and Glaucoma:* Prescribe QuilliChew ER to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Closely monitor patients with a history of increased IOP or open angle glaucoma. (5.10)
- *Motor and Verbal Tics, and Worsening of Tourette's Syndrome:* Before initiating QuilliChew ER, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome. Discontinue treatment if clinically appropriate. (5.11)

### ADVERSE REACTIONS

Based on accumulated data from other methylphenidate products, the most common ( $\geq 5\%$  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 Tris Pharma, Inc. at (732) 940-0358 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Antihypertensive Drugs: Monitor blood pressure. Adjust dosage of antihypertensive drug as needed. (7)

See 17 for PATIENT COUNSELING INFORMATION and [Medication Guide](#).

Revised: 10/2023

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- 2.2 Recommended Dosage
- 2.3 Administration Instructions
- 2.4 Switching from other Methylphenidate Products
- 2.5 Dosage Reduction and Discontinuation

**3 DOSAGE FORMS AND STRENGTHS****4 CONTRAINDICATIONS**

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## FULL PRESCRIBING INFORMATION

### WARNING: ABUSE, MISUSE, AND ADDICTION

QuilliChew ER has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including QuilliChew ER, can result in overdose and death [see [Overdosage \(10\)](#)], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing QuilliChew ER, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug. Throughout QuilliChew ER treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction [see [Warnings and Precautions \(5.1\)](#) and [Drug Abuse and Dependence \(9.2\)](#)].

## 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 patients with 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 \(5.2\)](#)].
- the family history and clinically evaluate patients for motor or verbal tics or Tourette's syndrome before initiating QuilliChew ER [see [Warnings and Precautions \(5.10\)](#)].

### 2.2 Recommended Dosage

The recommended starting dosage 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.

## 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 \(11\)](#), [Clinical Pharmacology \(12.3\)](#)].

## 2.5 Dosage Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse reaction occur, reduce dosage, or, if necessary, discontinue QuilliChew ER. If improvement is not observed after appropriate dosage adjustment over a one-month period, discontinue QuilliChew ER.

# 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 Abuse, Misuse, and Addiction**

QuilliChew ER has a high potential for abuse and misuse. The use of QuilliChew ER exposes individuals to the risks of abuse and misuse, which can lead to the development of a substance use disorder, including addiction. QuilliChew ER can be diverted for non-medical use into illicit channels or distribution [see [Drug Abuse and Dependence \(9.2\)](#)]. Misuse and abuse of CNS stimulants, including QuilliChew ER, can result in overdose and death [see [Overdosage \(10\)](#)], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing QuilliChew ER, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks and proper disposal of any unused drug. Advise patients to store QuilliChew ER in a safe place, preferably locked, and instruct patients to not give QuilliChew ER to anyone else. Throughout QuilliChew ER treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

### **5.2 Risks to Patients with Serious Cardiac Disease**

Sudden death has occurred in patients with structural cardiac abnormalities or other serious cardiac disease who were treated with CNS stimulants at the recommended ADHD dosage.

Avoid QuilliChew ER use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac disease.

### **5.3 Increased Blood Pressure and Heart Rate**

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). Some patients may have larger increases.

Monitor all QuilliChew ER-treated 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 QuilliChew ER 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 the recommended dosage, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. 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% of placebo-treated patients. If such symptoms occur, consider discontinuing QuilliChew ER.

### **5.5 Priapism**

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate use in both adult and pediatric male patients. Although priapism was not reported with methylphenidate initiation, it developed after some time on methylphenidate, often subsequent to an increase in dosage. Priapism also occurred during a period of methylphenidate withdrawal (drug holidays or during discontinuation).

QuilliChew ER treated 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, sequelae have included digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports and at the therapeutic dosages of CNS stimulants in all age groups throughout the course of treatment. Signs and symptoms generally improved after dosage reduction or discontinuation of the CNS stimulant.

Careful observation of digital changes is necessary during QuilliChew ER treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for QuilliChew ER-treated patients who develop signs or symptoms of peripheral vasculopathy.

### **5.7 Long-Term Suppression of Growth in Pediatric Patients**

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 pediatric patients who received methylphenidate for 7 days per week throughout the year had 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 development period.

Closely monitor growth (weight and height) in QuilliChew ER-treated pediatric patients. Pediatric 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.

## 5.9 Acute Angle Closure Glaucoma

There have been reports of angle closure glaucoma associated with methylphenidate treatment. Although the mechanism is not clear, QuilliChew ER -treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist.

## 5.10 Increased Intraocular Pressure and Glaucoma

There have been reports of an elevation of intraocular pressure (IOP) associated with methylphenidate treatment [*see [Adverse Reactions \(6.2\)](#)*].

Prescribe QuilliChew ER to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Closely monitor QuilliChew ER -treated patients with a history of abnormally increased IOP or open angle glaucoma.

## 5.11 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 [*see [Adverse Reactions \(6.2\)](#)*].

Before initiating QuilliChew ER, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor QuilliChew ER-treated patients for the emergence or worsening of tics or Tourette's syndrome, and discontinue treatment if clinically appropriate.

## 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 \(7.1\)](#)*]
- Abuse, Misuse, and Addiction [*see [Boxed Warning](#), [Warnings and Precautions \(5.1\)](#), [Drug Abuse and Dependence \(9.2, 9.3\)](#)*]
- Risks to Patients with Serious Cardiac Disease [*see [Warnings and Precautions \(5.2\)](#)*]

- Increased Blood Pressure and Heart Rate [*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 in Pediatric Patients [*see [Warnings and Precautions \(5.7\)](#)*]
- Risks in Phenylketonuria [*see [Warnings and Precautions \(5.8\)](#)*]
- Acute Angle Closure Glaucoma [*see [Warnings and Precautions \(5.9\)](#)*]
- Increased Intraocular Pressure and Glaucoma [*see [Warnings and Precautions \(5.10\)](#)*]
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome [*see [Warnings and Precautions \(5.11\)](#)*]

## 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.

### Adverse Reactions in Studies with Other Methylphenidate Products in Children, Adolescents, and Adults with ADHD

Commonly reported ( $\geq 2\%$  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.

### Adverse Reactions in Studies 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 ( $\geq 2\%$  in the QuilliChew ER group and greater than placebo) adverse reactions reported in the double-blind, randomized, placebo-controlled phase in patients optimized to doses of QuilliChew ER 20 to 60 mg/day are described in Table 1.

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

<b>Adverse reaction</b>	<b>QuilliChew ER</b> N= 42 n (%)	<b>Placebo</b> 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, Increased intraocular pressure, 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, Motor and Verbal Tics

*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**

#### **MAOI 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.

#### **Antihypertensive Drugs**

QuilliChew ER may decrease the effectiveness of drugs used to treat hypertension. Monitor blood pressure and adjust the dosage of the hypertensive drug as needed [*see [Warnings and Precautions \(5.3\)](#)*].

#### **Halogenated Anesthetics**

Concomitant use of halogenated anesthetics and QuilliChew ER may increase the risk of sudden blood pressure and heart rate increase during surgery. Avoid use of QuilliChew ER in patients being treated with anesthetics on the day of surgery.

#### **Risperidone**

Combined use of methylphenidate with risperidone when there is a change, whether an increase or decrease, in dosage of either or both medications, may increase the risk of extrapyramidal symptoms (EPS). Monitor for signs of EPS.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### *Pregnancy Exposure Registry*

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visiting

online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/othermedications/>.

### 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% to 4% and 15% to 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<sup>2</sup> basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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 safety and effectiveness of QuilliChew ER in pediatric patients less than 6 years have not been established.

The long-term efficacy of methylphenidate in pediatric patients has 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  $\text{mg}/\text{m}^2$  basis.

In the study conducted in young rats, methylphenidate was administered orally at doses of up to 100  $\text{mg}/\text{kg}/\text{day}$  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 to 14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50  $\text{mg}/\text{kg}/\text{day}$  (approximately 6 times the maximum recommended human dose [MRHD] on a  $\text{mg}/\text{m}^2$  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  $\text{mg}/\text{m}^2$  basis). The no effect level for juvenile neurobehavioral development in rats was 5  $\text{mg}/\text{kg}/\text{day}$  (half the MRHD on a  $\text{mg}/\text{m}^2$  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

QuilliChew ER has a high potential for abuse and misuse which can lead to the development of a substance use disorder, including addiction [see [Warnings and Precautions \(5.1\)](#)].

QuilliChew ER can be diverted for non-medical use into illicit channels or distribution.

Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of methylphenidate may cause increased heart rate, respiratory rate, or blood pressure; sweating; dilated pupils; hyperactivity; restlessness; insomnia; decreased appetite; loss of coordination; tremors; flushed skin; vomiting; and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including QuilliChew ER, can result in overdose and death [see [Overdosage \(10\)](#)], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

### 9.3 Dependence

#### Physical Dependence

QuilliChew ER may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal signs and symptoms after abrupt discontinuation or dose reduction following prolonged use of CNS stimulants including QuilliChew ER include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

#### Tolerance

QuilliChew ER may produce tolerance. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).



## 10 OVERDOSAGE

### Clinical Effects of Overdose

Overdose of CNS stimulants is characterized by the following sympathomimetic effects:

- Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden cardiac death. Takotsubo cardiomyopathy may develop.
- CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin syndrome, seizures, cerebral vascular accidents, and coma may occur.
- Life-threatening hyperthermia (temperatures greater than 104°F) and rhabdomyolysis may develop.

### Overdose Management

Consider the possibility of multiple drug ingestion. The pharmacokinetic profile of QuilliChew ER should be considered when treating patients with overdose. Because methylphenidate has a large volume of distribution and is rapidly metabolized, dialysis is not useful. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

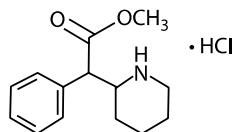
## 11 DESCRIPTION

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  $\alpha$ -phenyl-2-piperidineacetate hydrochloride, and its structural formula is shown in Figure 1.

**Figure 1: Methylphenidate HCl structure**



$C_{14}H_{19}NO_2 \cdot HCl$

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

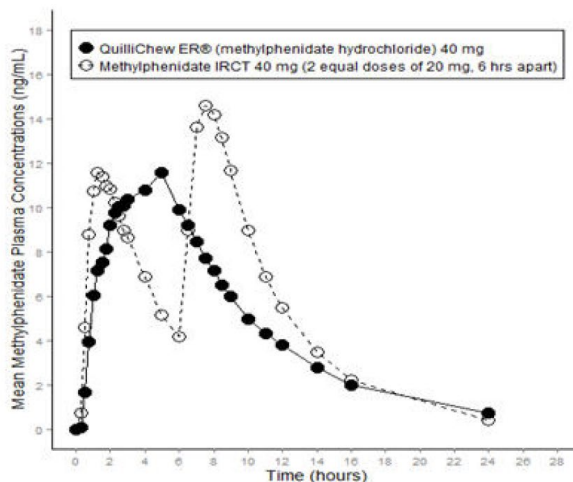
Methylphenidate is a racemic mixture comprised of the *d*- and *l*-isomers. The *d*-isomer is more pharmacologically active than the *l*-isomer. The mode of therapeutic action in ADHD is not known. Methylphenidate blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increases 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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.

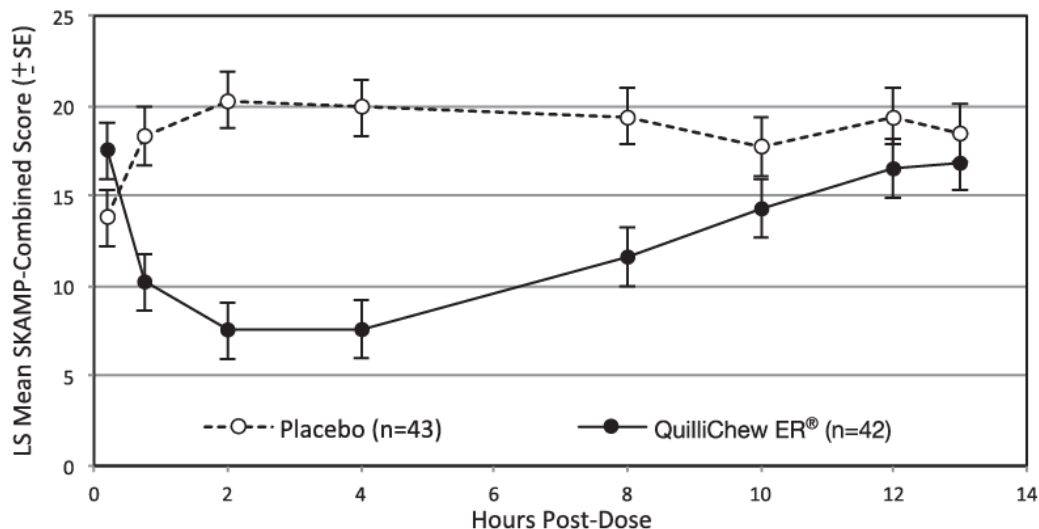
**Table 2: Primary Efficacy Result (ITT Population)**

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 <sup>a</sup> (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.

<sup>a</sup>Least-Squares Mean Difference (drug minus placebo).

**Figure 3: SKAMP-Combined Scores Over Time (LS Mean  $\pm$ 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-24478-074-01	NP 12
Bottles of 100	30 mg	NDC-24478-075-01	NP 13
Bottles of 100	40 mg	NDC-24478-076-01	NP 14

## 16.2 Storage and Handling

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

## 17 PATIENT COUNSELING INFORMATION

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

### Abuse, Misuse and Addiction

Educate patients and their families about the risks of abuse, misuse, and addiction of QuilliChew ER, which can lead to overdose and death, and proper disposal of any unused drug [see [Warnings and Precautions \(5.1\)](#), [Drug Abuse and Dependence \(9.2\)](#), [Overdosage \(10\)](#)]. Advise patients to store QuilliChew ER in a safe place, preferably locked, and instruct patients to not give QuilliChew ER to anyone else.

### Dosage and Administration Instructions

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

### Risks to Patients with Serious Cardiac Disease

Advise patients that there are potential risks to patients with serious cardiac disease, including sudden death, 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 \(5.2\)](#)].

### Increased Blood Pressure and Heart Rate

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

### Psychiatric Adverse Reactions

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 \(5.6\)](#)].

#### Long-Term Suppression of Growth in Pediatric Patients

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 \(5.8\)](#)].

#### Increased Intraocular Pressure (IOP) and Glaucoma

Advise patients that IOP and glaucoma may occur during treatment with QuilliChew ER [see [Warnings and Precautions \(5.9\)](#)].

#### Motor and Verbal Tics, and Worsening of Tourette’s Syndrome

Advise patients that motor and verbal tics and worsening of Tourette’s Syndrome may occur during treatment with QuilliChew ER. Instruct patients to notify their healthcare provider if emergence of new tics or worsening of tics or Tourette’s syndrome occurs [see [Warnings and Precautions \(5.10\)](#)].

#### Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in females exposed to QuilliChew ER during pregnancy [see [Use in Specific Populations \(8.1\)](#)].

#### Lactation

Advise nursing mother to monitor infants exposed to QuilliChew ER through breastmilk for agitation, poor feeding, and reduced weight gain [see [Use in Specific Populations \(8.2\)](#)].

This product’s label may have been updated. For current full prescribing information, please visit [www.trispharma.com](http://www.trispharma.com).

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Manufactured by:

**Tris Pharma, Inc.**

Monmouth Junction, NJ 08852

LB8533

Rev.02

**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 may cause serious side effects, including:**

- **Abuse, misuse, and addiction.** QuilliChew ER has a high chance for abuse and misuse and may lead to substance use problems, including addiction. Misuse and abuse of QuilliChew ER, other methylphenidate containing medicines, and amphetamine containing medicines, can lead to overdose and death. The risk of overdose and death is increased with higher doses of QuilliChew ER or when it is used in ways that are not approved, such as snorting or injection.
- Your healthcare provider should check you or your child's risk for abuse, misuse, and addiction before starting treatment with QuilliChew ER and will monitor you or your child during treatment.
- QuilliChew ER may lead to physical dependence after prolonged use, even if taken as directed by your healthcare provider.
- Do not give QuilliChew ER to anyone else. See “**What is QuilliChew ER?**” for more information.
- Keep QuilliChew ER in a safe place and properly dispose of any unused medicine. See “**How should I store QuilliChew ER?**” for more information.
- Tell your healthcare provider if you or your child have ever abused or been dependent on alcohol, prescription medicines, or street drugs.
  
- **Risks for people with serious heart disease.** Sudden death has happened in people who have heart defects or other serious heart disease.

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

Tell your healthcare provider if you or your child have any heart disease, or heart defects.

**Call your healthcare provider or go to the nearest hospital emergency room 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.**

- **Increased blood pressure and heart rate.**

Your health care provider should check your or your child's blood pressure and heart rate regularly during treatment with QuilliChew ER.

**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 healthcare 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.**

### **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.

**QuilliChew ER is a federally controlled substance (CII) because it contains methylphenidate that can be a target for people who abuse prescription medicines or street drugs.** Keep QuilliChew ER in a safe place to protect it from theft. Never give your QuilliChew ER to anyone else, because it may cause death or harm them. Selling or giving away QuilliChew ER may harm others and is against the law.

### **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 disease, heart defects, or high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- circulation problems in fingers and toes
- have eye problems, including increased pressure in your eye, glaucoma, or problems with your close-up vision (farsightedness)
- have or had repeated movements or sounds (tics) or Tourette's syndrome, or have a family history of tics or Tourette's syndrome
- 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.
  - There is a pregnancy registry for females who are exposed to ADHD medications during pregnancy. The purpose of the registry is to collect information about the health of females exposed to Quillichew ER and their baby. If you or your child becomes pregnant during treatment with Quillichew ER, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visit <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/othermedications/>.
- if you are breastfeeding or plan to breast feed. QuilliChew ER passes into your breast milk. You and your healthcare provider should decide if you will take QuilliChew ER or breastfeed.

**Tell your healthcare 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 healthcare provider will decide whether QuilliChew ER can be taken with other medicines.

**Especially tell your healthcare 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 healthcare 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.
- 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.
- If a dose is missed, you or your child should talk to your health care provider about dosing.

If you or your child take too much QuilliChew ER, call your healthcare provider or Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

**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 the 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.**
- **Circulation problems in fingers and toes (peripheral vasculopathy, including Raynaud’s phenomenon). Signs and symptoms may include:**
  - fingers or toes may feel numb, cool, painful
  - fingers or toes may change color from pale, to blue, to redTell your healthcare provider if you or your child have numbness, pain, skin color change, or sensitivity to temperature in your fingers or toes, or if you or your child have any signs of unexplained wounds appearing on fingers or toes during treatment with QuilliChew ER.
- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with QuilliChew ER. QuilliChew ER treatment may be stopped if your child is not gaining weight or height.
- **Eye problems (increased pressure in the eye and glaucoma).** Call your healthcare provider right away if you or your child develop changes in your vision or eye pain, swelling, or redness.
- **New or worsening tics or worsening Tourette’s syndrome.** Tell your healthcare provider if you or your child get any new or worsening tics or worsening Tourette’s syndrome during treatment with QuilliChew ER.

### The most common side effects of QuilliChew ER include:

<ul style="list-style-type: none"><li>• decreased appetite</li><li>• trouble sleeping</li><li>• nausea</li><li>• vomiting</li></ul>	<ul style="list-style-type: none"><li>• indigestion</li><li>• stomach pain</li><li>• weight loss</li><li>• anxiety</li><li>• dizziness</li><li>• irritability</li></ul>	<ul style="list-style-type: none"><li>• mood swings</li><li>• fast heart beat</li><li>• increased blood pressure</li></ul>
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These are not all the possible side effects of QuilliChew ER.

**Call your doctor 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).
- Dispose of remaining, unused, or expired QuilliChew ER by a medicine take-back program at a U.S. Drug Enforcement Administration (DEA) authorized collection site. If no take-back program or DEA authorized collector is available, mix QuilliChew ER with

an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away QuilliChew ER in the household trash. Visit [www.fda.gov/drugdisposal](http://www.fda.gov/drugdisposal) for additional information on disposal of unused medicines.

- **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 is written for healthcare 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.

Distributed by:

**NextWave Pharmaceuticals, Inc**

A subsidiary of Tris Pharma, Inc., Monmouth Junction, NJ 08852

Manufactured by:

**Tris Pharma, Inc.**, Monmouth Junction, NJ 08852

For more information, please contact Tris Pharma, Inc. at (732) 940-0358 or visit the website at [www.QuilliChewER.com](http://www.QuilliChewER.com).

This product's label may have been updated. For current full prescribing information, please visit [www.trispharma.com](http://www.trispharma.com).

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DYANAVEL<sup>®</sup> XR safely and effectively. See full prescribing information for DYANAVEL XR.

DYANAVEL<sup>®</sup> XR (amphetamine) extended-release oral suspension, CII

DYANAVEL<sup>®</sup> XR (amphetamine) extended-release tablets, for oral use, CII

Initial U.S. Approval: 1960

### WARNING: ABUSE, MISUSE, AND ADDICTION

See full prescribing information for complete boxed warning.

DYANAVEL XR has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including DYANAVEL XR, can result in overdose and death (5.1, 9.2, 10):

- Before prescribing DYANAVEL XR, assess each patient's risk for abuse, misuse, and addiction.
- Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug.
- Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

### RECENT MAJOR CHANGES

Boxed Warning	10/2023
Dosage and Administration (2.1, 2.2)	10/2023
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.6, 5.8)	10/2023

### INDICATIONS AND USAGE

DYANAVEL XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older (1)

### DOSAGE AND ADMINISTRATION

- Recommended starting dosage is 2.5 mg or 5 mg once daily in the morning (2.2)
- Dosage may be increased in increments of 2.5 mg to 10 mg per day every 4 to 7 days up to a maximum daily dose of 20 mg (2.2)
- May be taken with or without food (2.3)
- Extended-release oral suspension: Shake bottle before administering (2.3)
- Extended-release tablets: May be chewed or swallowed whole (2.3)
- DYANAVEL XR oral suspension can be substituted with DYANAVEL XR tablets on a milligram per milligram basis (2.4)
- Do not substitute for other amphetamine products on a milligram-per-milligram basis, because of different amphetamine salt compositions and differing pharmacokinetic profiles (2.4)

### DOSAGE FORMS AND STRENGTHS

- Extended-release oral suspension: containing 2.5 mg amphetamine base equivalents per mL (3)
- Extended-release tablets: 5 mg (functionally scored), 10 mg, 15 mg, 20 mg (3)

### CONTRAINDICATIONS

- Known hypersensitivity to amphetamine products or other ingredients in DYANAVEL XR (4)

- Use of monoamine oxidase inhibitor (MAOI) or within 14 days of the last MAOI dose (4, 7.1)

### WARNINGS AND PRECAUTIONS

- **Risks to Patients with Serious Cardiac Disease:** Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease (5.2)
- **Increased Blood Pressure and Heart Rate:** Monitor blood pressure and pulse. (5.3)
- **Psychiatric Adverse Reactions:** Prior to initiating DYANAVEL XR, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing DYANAVEL XR (5.4)
- **Long-Term Suppression of Growth in Pediatric Patients:** Closely monitor growth (height and weight) in pediatric patients. Pediatric patients not growing or gaining height or weight as expected may need to have their treatment interrupted (5.5)
- **Peripheral Vasculopathy, including Raynaud's phenomenon:** Careful observation for digital changes is necessary during DYANAVEL XR treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy (5.6)
- **Serotonin Syndrome:** Increased risk when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. If it occurs, discontinue DYANAVEL XR and initiate supportive treatment (5.7).
- **Motor and Verbal Tics, and Worsening of Tourette's Syndrome:** Before initiating DYANAVEL XR, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome. Discontinue treatment if clinically appropriate. (5.8)

### ADVERSE REACTIONS

Most common adverse reactions observed with amphetamine products: dry mouth, anorexia, weight loss, abdominal pain, nausea, insomnia, restlessness, emotional lability, dizziness, tachycardia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Tris Pharma, Inc. at 1-732-940-0358 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- **Acidifying and Alkalinizing Agents:** Agents that alter urinary pH can alter blood levels of amphetamine. Acidifying agents can decrease amphetamine blood levels, while alkalinizing agents can increase amphetamine blood levels. Adjust DYANAVEL XR dosage accordingly (2.5, 7.1)

### USE IN SPECIFIC POPULATIONS

- **Pregnancy:** May cause fetal harm (8.1)
- **Lactation:** Breastfeeding not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2023



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## FULL PRESCRIBING INFORMATION

### WARNING: ABUSE, MISUSE, AND ADDICTION

DYANAVEL XR has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including DYANAVEL XR, can result in overdose and death [see [Overdosage \(10\)](#)], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing DYANAVEL XR, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug. Throughout DYANAVEL XR treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction [see [Warnings and Precautions \(5.1\)](#), [Drug Abuse and Dependence \(9.2\)](#)].

## 1 INDICATIONS AND USAGE

DYANAVEL XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older [see [Clinical Studies \(14\)](#)].

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Pretreatment Screening

Prior to treating patients with DYANAVEL XR, 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 \(5.2\)](#)].
- the family history and clinically evaluate patients for motor or verbal tics or Tourette's syndrome before initiating DYANAVEL XR [see [Warnings and Precautions \(5.8\)](#)].

### 2.2 Recommended Dosage

The recommended starting dosage is 2.5 mg or 5 mg once daily in the morning. The dosage may be increased in increments of 2.5 mg to 10 mg per day every 4 to 7 days based on clinical response. The maximum recommended dosage is 20 mg once daily.

### 2.3 Administration Information

Administer DYANAVEL XR orally once daily in the morning with or without food.

#### *DYANAVEL XR Extended-Release Oral Suspension*

Instruct patients to read the "Instructions for Use" for complete administration instructions.

- Ensure that the bottle adapter is firmly inserted into the bottle and do not remove once inserted.
- Shake the bottle of DYANAVEL XR extended-release oral suspension well before every administration.
- Use with the oral dosing dispenser provided by the pharmacist.

#### *DYANAVEL XR Extended-Release Tablets*

- May be chewed or swallowed whole [see [Clinical Pharmacology \(12.3\)](#)].
- The 5 mg extended-release tablet is functionally scored and may be divided into equal halves (2.5 mg) at the score line.

### 2.4 Switching from Other Amphetamine Products

DYANAVEL XR extended-release oral suspension can be substituted with DYANAVEL XR extended-release tablets on a milligram-per-milligram basis [see [Clinical Pharmacology \(12.3\)](#)].

If switching from other amphetamine products, discontinue that treatment, and titrate with DYANAVEL XR using the above titration schedule. Do not substitute for other amphetamine products on a milligram-per-

milligram basis, because of different amphetamine salt compositions and differing pharmacokinetic profiles [see [Description \(11\)](#), [Clinical Pharmacology \(12.3\)](#)].

## 2.5 Dosage Modifications due to Drug Interactions

Agents that alter urinary pH can impact urinary excretion and alter blood levels of amphetamine. Acidifying agents (e.g., ascorbic acid) decrease blood levels, while alkalinizing agents (e.g., sodium bicarbonate) increase blood levels. Adjust DYANAVEL XR dosage accordingly [see [Drug Interactions \(7.1\)](#)].

## 3 DOSAGE FORMS AND STRENGTHS

*DYANAVEL XR (amphetamine) extended-release oral suspension:*

- Extended-release oral suspension contains 2.5 mg amphetamine base equivalents per mL.

*DYANAVEL XR (amphetamine) extended-release tablets:*

- 5 mg: Off-white, speckled, caplet shaped tablet with '5' debossed on one side and functionally scored on the other side
- 10 mg: Off-white, speckled, diamond shaped tablet with '10' debossed on one side and plain on the other side
- 15 mg: Off-white, speckled, triangle shaped tablet with '15' debossed on one side and plain on the other side
- 20 mg: Off-white, speckled, oval shaped tablet with '20' debossed on one side and plain on the other side

All strengths are expressed in terms of amphetamine base equivalents.

## 4 CONTRAINDICATIONS

DYANAVEL XR is contraindicated:

- In patients known to be hypersensitive to amphetamine, or other components of DYANAVEL XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other amphetamine products [see [Adverse Reactions \(6\)](#)].
- Patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis [see [Warnings and Precautions \(5.7\)](#), [Drug Interactions \(7.1\)](#)].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Abuse, Misuse, and Addiction

DYANAVEL XR has a high potential for abuse and misuse. The use of DYANAVEL XR exposes individuals to the risks of abuse and misuse, which can lead to the development of a substance use disorder, including addiction. DYANAVEL XR can be diverted for non-medical use into illicit channels or distribution [see [Drug Abuse and Dependence \(9.2\)](#)]. Misuse and abuse of CNS stimulants, including DYANAVEL XR, can result in overdose and death [see [Overdosage \(10\)](#)], and this risk is increased with higher doses and or unapproved methods of administration, such as snorting or injection.

Before prescribing DYANAVEL XR, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks and proper disposal of any unused drug. Advise patients to store DYANAVEL XR in a safe place, preferably locked, and instruct patients to not give DYANAVEL XR to anyone else. Throughout DYANAVEL XR treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

### 5.2 Risks for Patients with Serious Cardiac Disease

Sudden death has been reported in patients with structural cardiac abnormalities or other serious cardiac disease who were treated with CNS stimulants at the recommended ADHD dosages.

Avoid DYANAVEL XR use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease.

### **5.3 Increased Blood Pressure and Heart Rate**

CNS stimulants cause an increase in blood pressure (mean increase about 2 to 4 mm Hg) and heart rate (mean increase about 3 to 6 bpm).

Monitor all DYANAVEL XR-treated patients for potential tachycardia and hypertension.

### **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 Disease*

CNS stimulants may induce a manic or mixed episode in patients with bipolar disorder. Prior to initiating DYANAVEL XR 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 the recommended dosage, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without prior history of psychotic illness or mania. 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% of placebo-treated patients. If such symptoms occur, consider discontinuing DYANAVEL XR.

### **5.5 Long-Term Suppression of Growth in Pediatric Patients**

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in DYANAVEL XR treated pediatric patients treated with CNS stimulants.

Pediatric patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

### **5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon**

CNS stimulants, including DYANAVEL XR, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, sequelae have included digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports and at the therapeutic dosage of CNS stimulants in all age groups throughout the course of treatment. Signs and symptoms generally improved after dosage reduction or discontinuation of the CNS stimulant.

Careful observation for digital changes is necessary during DYANAVEL XR treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for DYANAVEL XR-treated patients who develop signs or symptoms of peripheral vasculopathy.

### **5.7 Serotonin Syndrome**

Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are used in combination with other drugs that affect the serotonergic neurotransmitter systems such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort [see [Drug Interactions \(7.1\)](#)]. The co-administration with cytochrome P450 2D6 (CYP2D6) inhibitors may also increase the risk with increased exposure to DYANAVEL XR. In these situations, consider an alternative non-serotonergic drug or an alternative drug that does not inhibit CYP2D6 [see [Drug Interactions \(7.1\)](#)].

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Concomitant use of DYANAVEL XR with MAOI drugs is contraindicated [see [Contraindications \(4\)](#)].

Discontinue treatment with DYANAVEL XR and any concomitant serotonergic agents immediately if symptoms of serotonin syndrome occur, and initiate supportive symptomatic treatment. If concomitant use of DYANAVEL XR with other serotonergic drugs or CYP2D6 inhibitors is clinically warranted, initiate DYANAVEL XR with lower doses, monitor patients for the emergence of serotonin syndrome during drug initiation or titration, and inform patients of the increased risk for serotonin syndrome.

### 5.8 Motor and Verbal Tics, and Worsening of Tourette's Syndrome

CNS stimulants, including amphetamine, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported [see [Adverse Reactions \(6.2\)](#)].

Before initiating DYANAVEL XR, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor DYANAVEL XR-treated patients for the emergence or worsening of tics or Tourette's syndrome, and discontinue treatment if clinically appropriate.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Abuse, Misuse, and Addiction [see [Boxed Warning, Warnings and Precautions \(5.1\)](#), and [Drug Abuse and Dependence \(9.2, 9.3\)](#)]
- Hypersensitivity to amphetamine, or other components of DYANAVEL XR [see [Contraindications \(4\)](#)]
- Hypertensive Crisis When Used Concomitantly with Monoamine Oxidase Inhibitors [see [Contraindications \(4\)](#) and [Drug Interactions \(7.1\)](#)]
- Risks to Patients with Serious Cardiac Disease [see [Warnings and Precautions \(5.2\)](#)]
- Increased Blood Pressure and Heart Rate [see [Warnings and Precautions \(5.3\)](#)]
- Psychiatric Adverse Reactions [see [Warnings and Precautions \(5.4\)](#)]
- Long-Term Suppression of Growth in Pediatric Patients [see [Warnings and Precautions \(5.5\)](#)]
- Peripheral Vasculopathy, including Raynaud's phenomenon [see [Warnings and Precautions \(5.6\)](#)]
- Serotonin Syndrome [see [Warnings and Precautions \(5.7\)](#)]
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome [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.

#### *Adverse Reactions in Studies with Other Amphetamine Products in Pediatric Patients and Adults with ADHD*

**Cardiovascular:** Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

**Central Nervous System:** Psychotic episodes at recommended doses, overstimulation, restlessness, irritability, euphoria, dyskinesia, dysphoria, depression, tremor, tics, aggression, anger, logorrhea.

**Eye Disorders:** Vision blurred, mydriasis.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.

Allergic: Urticaria, rash, hypersensitivity reactions including angioedema and anaphylaxis. Serious skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Endocrine: Impotence, changes in libido.

Skin: Alopecia.

#### *Adverse Reactions in Studies with DYANAVEL XR in Pediatric Patients with ADHD*

There is limited experience with DYANAVEL XR in controlled trials. Based on this limited experience, the adverse reaction profile of DYANAVEL XR appears similar to other amphetamine extended-release products. The most common ( $\geq 2\%$  in the DYANAVEL XR group and greater than placebo) adverse reactions reported in the Phase 3 controlled study conducted with DYANAVEL XR extended-release oral suspension in 108 patients with ADHD (aged 6 to 12 years) were: epistaxis, allergic rhinitis, and upper abdominal pain.

**Table 1. Common Adverse Reactions Occurring in  $\geq 2\%$  of Patients on DYANAVEL XR Extended-Release Oral Suspension and Greater than Placebo During the Double Blind Phase.**

Preferred Term	DYANAVEL XR (N=52)	Placebo (N=48)
<i>Respiratory, thoracic and mediastinal disorders</i>		
Epistaxis	3.8%	0%
Rhinitis allergic	3.8%	0%
<i>Gastrointestinal disorders</i>		
Abdominal pain upper	3.8%	2.1%

## **6.2 Postmarketing Experience**

The following adverse reactions have been identified during post approval use of other amphetamine 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.

Allergic: urticaria, rash, hypersensitivity reactions including angioedema and anaphylaxis. Serious skin rashes, including Stevens-Johnson Syndrome and toxic epidermal necrolysis have been reported

Cardiovascular: palpitations, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use

Central Nervous System: restlessness, irritability, euphoria, dyskinesia, dysphoria, depression, tremor, aggression, anger, logorrhea, and paresthesia (including formication), motor and verbal tics

Endocrine: impotence, changes in libido, frequent or prolonged erections

Eye Disorders: vision blurred, mydriasis

Gastrointestinal: unpleasant taste, constipation, intestinal ischemia, and other gastrointestinal disturbances

Musculoskeletal, Connective Tissue, and Bone Disorders: rhabdomyolysis

Psychiatric Disorders: dermatillomania, bruxism

Skin: alopecia

Vascular Disorders: Raynaud's phenomenon

## 7 DRUG INTERACTIONS

### 7.1 Drugs Having Clinically Important Interactions with Amphetamines

Table 2. Drugs having clinically important interactions with amphetamines.

<b>MAO Inhibitors (MAOI)</b>	
Clinical Impact	MAOI antidepressants slow amphetamine metabolism, increasing amphetamines effect on the release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of hypertensive crisis. Toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Intervention	Do not administer DYANAVEL XR concomitantly or within 14 days following administration of MAOI [see <a href="#">Contraindications (4)</a> and <a href="#">Warnings and Precautions (5.7)</a> ].
<b>Serotonergic Drugs</b>	
Clinical Impact	The concomitant use of DYANAVEL XR and serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome, particularly during DYANAVEL XR initiation or dosage increase. If serotonin syndrome occurs, discontinue DYANAVEL XR and the concomitant serotonergic drug(s) [see <a href="#">Warnings and Precautions (5.7)</a> ].
<b>CYP2D6 Inhibitors</b>	
Clinical Impact	The concomitant use of DYANAVEL XR and CYP2D6 inhibitors may increase the exposure of DYANAVEL XR compared to the use of the drug alone and increase the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during DYANAVEL XR initiation and after a dosage increase. If serotonin syndrome occurs, discontinue DYANAVEL XR and the CYP2D6 inhibitor [see <a href="#">Warnings and Precautions (5.7)</a> , <a href="#">Overdosage (10)</a> ].
<b>Alkalinizing Agents (Urinary and Gastrointestinal)</b>	
Clinical Impact	Increase blood levels and potentiate the action of amphetamine.
Intervention	Co-administration of DYANAVEL XR and gastrointestinal or urinary alkalinizing agents should be avoided.
<b>Acidifying Agents (Urinary and Gastrointestinal)</b>	
Clinical Impact	Lower blood levels and efficacy of amphetamines.
Intervention	Increase dose based on clinical response.
<b>Tricyclic Antidepressants</b>	

Clinical Impact	May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of <i>d</i> -amphetamine in the brain; cardiovascular effects can be potentiated.
Intervention	Monitor frequently and adjust or use alternative therapy based on clinical response.

## 7.2 Drug/Laboratory Test Interactions

Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### *Pregnancy Exposure Registry*

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DYANAVEL XR during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visiting online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/othermedications/>.

#### *Risk Summary*

There are limited published data on the use of amphetamines in pregnant women. These data are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines. No effects on morphological development were observed in embryo-fetal development studies with oral administration of amphetamine to rats and rabbits during organogenesis at doses that are approximately 3 and 16 times, respectively, the maximum recommended human dose (MRHD) of 20 mg/day (as base equivalents) on a mg/m<sup>2</sup> basis, given to adults. However, long-term neurochemical and behavioral effects have been reported in published animal developmental studies using clinically relevant doses of amphetamine [see *Data*]. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

#### *Clinical Considerations*

##### Fetal/Neonatal adverse reactions

Amphetamines, such as DYANAVEL XR, may cause vasoconstriction, including vasoconstriction of placental blood vessels, and may increase the risk for intrauterine growth restriction. In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. Premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

Monitor infants born to mothers taking amphetamines for symptoms of withdrawal, such as feeding difficulties, irritability, agitation, and excessive drowsiness.

#### *Data*

##### Animal Data

Amphetamine (*d*- to *l*- enantiomer ratio of 3:1) had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 3 and 16 times, respectively, the MRHD of 20 mg/day (as base equivalents) on a mg/m<sup>2</sup> basis, given to adults. Fetal malformations and death have been reported in mice following parenteral administration of *d*-amphetamine doses of 50 mg/kg/day (approximately 12 times the MRHD) given to adults on a mg/m<sup>2</sup> basis or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.



A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (*d*- or *d, l*-), at doses similar to those used clinically, can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

## **8.2 Lactation**

### *Risk Summary*

Based on limited case reports in published literature, amphetamine (*d*- or *d, l*-) is present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant and no effects on milk production. However, long term neurodevelopmental effects on infants from stimulant exposure are unknown. Because of the potential for serious adverse reactions in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with DYANAVEL XR.

## **8.4 Pediatric Use**

The safety and effectiveness have been established in pediatric patients with ADHD ages 6 to 17 years [see [Adverse Reactions \(6.1\)](#), [Clinical Pharmacology \(12\)](#), and [Clinical Studies \(14\)](#)].

The safety and efficacy of DYANAVEL XR in pediatric patients less than 6 years have not been established.

### *Long-Term Growth Suppression*

Growth should be monitored during treatment with stimulants, including DYANAVEL XR, and pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted [see [Warnings and Precautions \(5.5\)](#)].

## **8.5 Geriatric Use**

DYANAVEL XR has not been studied in the geriatric population.

# **9 DRUG ABUSE AND DEPENDENCE**

## **9.1 Controlled Substance**

DYANAVEL XR contains amphetamine, a Schedule II controlled substance.

## **9.2 Abuse**

DYANAVEL XR has a high potential for abuse and misuse which can lead to the development of a substance use disorder, including addiction [see [Warnings and Precautions \(5.1\)](#)]. DYANAVEL XR can be diverted for non-medical use into illicit channels or distribution.

Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of amphetamine may cause increased heart rate, respiratory rate, or blood pressure; sweating; dilated pupils; hyperactivity; restlessness; insomnia; decreased appetite; loss of coordination; tremors; flushed skin; vomiting; and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including DYANAVEL XR, can result in overdose and death [see [Overdosage \(10\)](#)], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

### 9.3 Dependence

#### *Physical Dependence*

DYANAVEL XR may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal signs and symptoms after abrupt discontinuation or dose reduction following prolonged use of CNS stimulants including DYANAVEL XR include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

#### *Tolerance*

DYANAVEL XR may produce tolerance. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

## 10 OVERDOSAGE

### Clinical Effects of Overdose

Overdose of CNS stimulants is characterized by the following sympathomimetic effects:

- Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden cardiac death. Takotsubo cardiomyopathy may develop.
- CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin syndrome, seizures, cerebral vascular accidents, and coma may occur.
- Life-threatening hyperthermia (temperatures greater than 104°F) and rhabdomyolysis may develop.

### Overdose Management

Consider the possibility of multiple drug ingestion. The pharmacokinetic profile of DYANAVEL XR should be considered when treating patients with overdose. D-amphetamine is not dialyzable. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

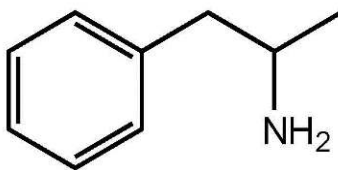
## 11 DESCRIPTION

DYANAVEL XR (amphetamine) extended-release oral suspension and DYANAVEL XR (amphetamine) extended-release tablets contain amphetamine, a CNS stimulant, in a 3.2:1 ratio of *d*- to *l*- amphetamine.

There are three active ingredients: amphetamine (complexed with sodium polystyrene sulfonate), dextroamphetamine sulfate and amphetamine aspartate. The dosage strengths are expressed in terms of amphetamine base.

DYANAVEL XR contains both immediate-release and extended-release components.

Structural Formula:



C<sub>9</sub>H<sub>13</sub>N MW 135.21

### Active Ingredients:

DYANAVEL XR extended-release oral suspension 2.5 mg/mL:

- Each 1 mL contains 2 mg of amphetamine (in a 3.2 to 1 ratio of *d*- to *l*-amphetamine complexed with sodium polystyrene sulfonate), and 0.5 mg amphetamine (present as 0.5 mg of amphetamine aspartate and 0.3 mg of dextroamphetamine sulfate).

DYANAVEL XR extended-release tablets:

- Each 5 mg strength tablet contains 4 mg of amphetamine (in a 3.2 to 1 ratio of *d*- to *l*-amphetamine complexed with sodium polystyrene sulfonate), and 1 mg of amphetamine (present as 1 mg of amphetamine aspartate and 0.7 mg of dextroamphetamine sulfate).
- Each 10 mg strength tablet contains 8 mg of amphetamine (in a 3.2 to 1 ratio of *d*- to *l*-amphetamine complexed with sodium polystyrene sulfonate), and 2 mg of amphetamine (present as 2 mg amphetamine aspartate and 1.4 mg dextroamphetamine sulfate).
- Each 15 mg strength tablet contains 12 mg of amphetamine (in a 3.2 to 1 ratio of *d*- to *l*-amphetamine complexed with sodium polystyrene sulfonate), and 3 mg of amphetamine (present as 3 mg amphetamine aspartate and 2 mg dextroamphetamine sulfate).
- Each 20 mg strength tablet contains 16 mg of amphetamine (in a 3.2 to 1 ratio of *d*- to *l*-amphetamine complexed with sodium polystyrene sulfonate), and 4 mg of amphetamine (present as 4 mg amphetamine aspartate and 2.7 mg dextroamphetamine sulfate).

DYANAVEL XR extended-release oral suspension and DYANAVEL XR extended-release tablets are intended for oral administration.

### Inactive Ingredients:

DYANAVEL XR extended-release oral suspension: anhydrous citric acid, bubblegum flavor, glycerin, methylparaben, modified starch, polysorbate 80, povidone, polyvinyl acetate, propylparaben, sodium lauryl sulfate, sodium polystyrene sulfonate, sucralose, triacetin and xanthan gum.

DYANAVEL XR extended-release tablets: bubblegum flavor, crospovidone, guar gum, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl acetate, povidone, silicon dioxide, sodium polystyrene sulfonate, sucralose, talc, triacetin and xanthan gum.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in ADHD is not known.

### 12.2 Pharmacodynamics

Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extra neuronal space.

### 12.3 Pharmacokinetics

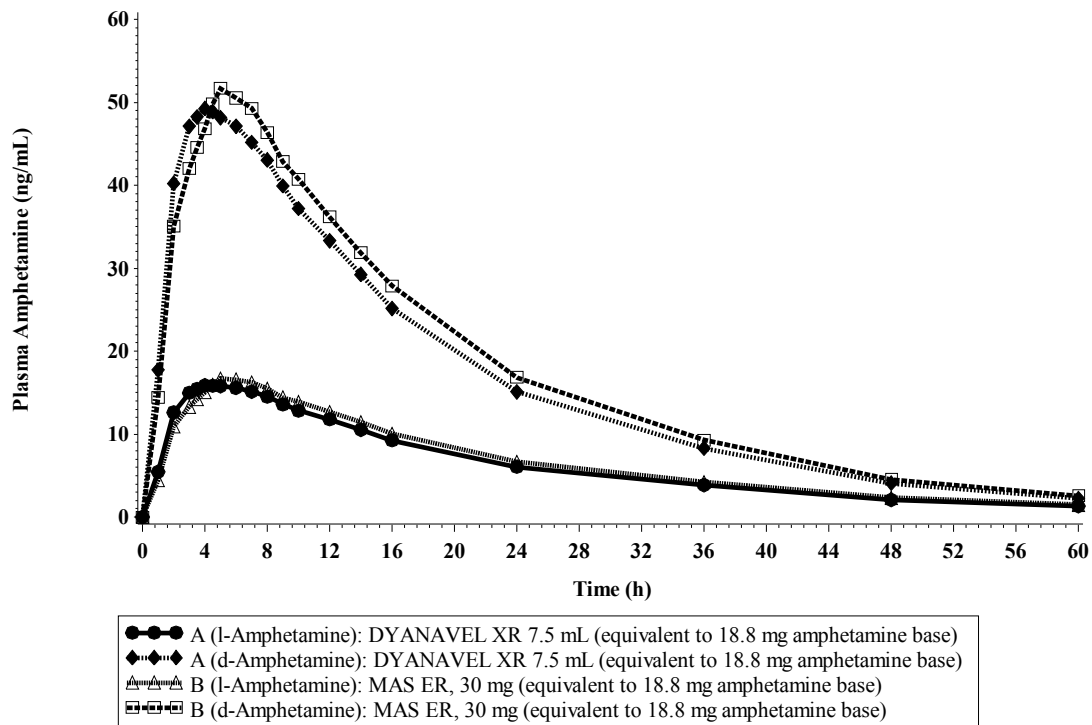
## Absorption

### Extended-Release Oral Suspension

Following a single 18.8 mg dose of DYANAVEL XR extended-release oral suspension in 29 healthy adult subjects under fasting conditions in a crossover study, the median (range) time to peak plasma concentrations ( $T_{max}$ ) for both *d*- and *l*- isomers of amphetamine were 4 (2 to 7) hours after dosing. Peak concentrations ( $C_{max}$ ) of *d*- and *l*-amphetamine were 102% and 106%, respectively, of the  $C_{max}$  of immediate-release (IR) mixed amphetamine salts (MAS) tablets. The relative bioavailability of DYANAVEL XR compared with an equal dose of IR MAS tablets is 106% for *d*- and 111% for *l*-amphetamine.

Following a single 18.8 mg dose of DYANAVEL XR extended-release oral suspension in 28 healthy adult subjects in a crossover study under fasting conditions, the median (range) time to peak plasma concentrations ( $T_{max}$ ) were about 4 (2 to 7) hours and 5 (3 to 7) hours for *d*- and *l*-amphetamine, respectively. Peak concentration ( $C_{max}$ ) was 93% and 94%, respectively, of the  $C_{max}$  of extended release (ER) MAS capsules. The relative bioavailability of DYANAVEL XR compared with an equal dose of ER MAS capsules is 94% for both *d*- and *l*-amphetamine.

**Figure 1. Mean *d*- and *l*-Amphetamine Plasma Concentration-Time Profile Following Administration of a Single Dose (18.8 mg amphetamine base) of DYANAVEL XR Extended-Release Oral Suspension and MAS ER Under Fasting Conditions**



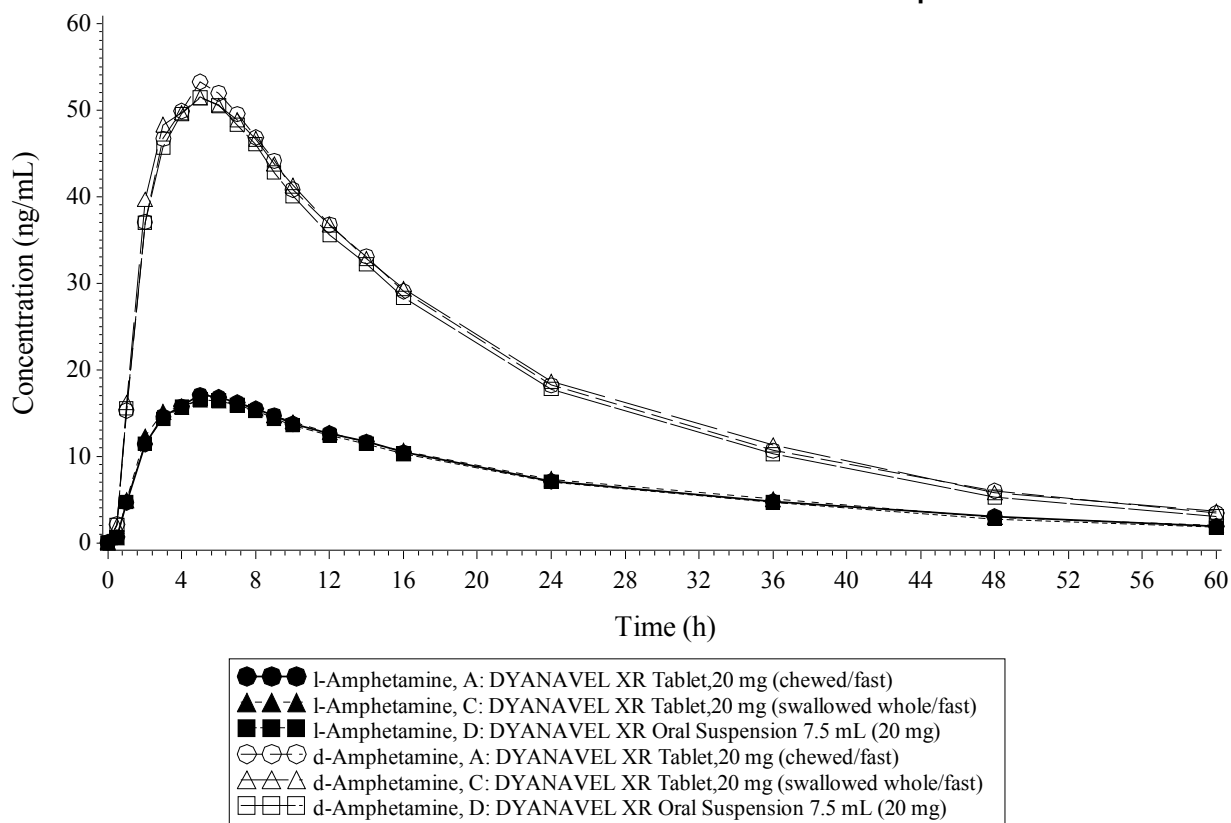
### Extended-Release Tablet

Following a single 20 mg dose of DYANAVEL XR extended-release tablets (swallowed whole) to 36 healthy adults under fasted conditions in a crossover study, the median (range) time to peak plasma concentration ( $T_{max}$ ) for both *d*- and *l*-amphetamine, were 5.0 (2 to 9) hours after dosing. Peak concentrations ( $C_{max}$ ) for both *d*- and *l*-amphetamine, were 101% of the  $C_{max}$  of DYANAVEL XR oral

suspension. The relative bioavailability of DYANAVEL XR tablets compared with an equal dose of DYANAVEL XR oral suspension, for *d*- and *l*-amphetamine, were 105% and 106%, respectively.

Dyanavel XR extended-release tablets chewed or swallowed whole under fasted conditions did not significantly affect exposure and  $T_{max}$ .

**Figure 2. Mean Plasma *d*- and *l*-Amphetamine Concentration-Time Profiles for DYANAVEL XR Extended-Release Tablet and DYANAVEL XR Extended-Release Oral Suspension**



**Effect of Food**

**Extended-Release Oral Suspension**

Ingestion of 18.8 mg of DYANAVEL XR extended-release oral suspension with a high-fat meal increased the average  $C_{max}$  of both isomers of DYANAVEL XR by about 2%, decreased the AUC of *d*- and *l*-amphetamine by 5.7% and 7.4%, respectively. A delay of  $T_{max}$  by approximately 1 hour was observed for both isomers.

**Extended-Release Tablet**

Ingestion of 20 mg DYANAVEL XR extended-release tablets with a high-fat meal decreased the average  $C_{max}$  of both isomers of amphetamine by about 3%, decreased AUC of *d*- and *l*-amphetamine by about 4.0% and 7.3%, respectively. Median  $T_{max}$  was not delayed for either isomer.

**Elimination**

The mean plasma terminal elimination half-lives of *d*- and *l*-amphetamine were 12.4 hours and 15.1 hours, respectively, following a single 18.8 mg dose of DYANAVEL XR extended-release oral suspension.

The mean plasma terminal elimination half-lives of *d*- and *l*-amphetamine were 13.5 hours and 17.3 hours, respectively, following a single 20 mg dose of DYANAVEL XR extended-release tablets.

### *Metabolism*

Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4-hydroxyamphetamine, or on the side chain A or B carbons to form alpha-hydroxy-amphetamine or norephedrine, respectively. Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Because CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

### *Excretion*

With normal urine pH, approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30%-40% of the dose is recoverable in urine as amphetamine itself.

### Specific Populations

#### *Pediatric Patients*

Following a single 10 mg dose of DYANAVEL XR extended-release oral suspension in pediatric subjects with ADHD (aged 6 to 12 years) under fasting conditions, peak plasma concentrations of *d*- and *l*-amphetamine occurred at a median time of 3.9 and 4.5 hours after dosing, respectively. The mean plasma terminal elimination half-lives of *d*- and *l*-amphetamine were 10.4 hours and 12.1 hours, respectively.

#### *Patients with Hepatic or Renal Impairment*

No specific studies have been conducted to evaluate the effect of renal impairment or hepatic impairment on the PK after DYANAVEL XR administration. However, urinary recovery of amphetamine has been reported to range from 1% to 75%, depending on urinary pH, with the remaining fraction of the dose hepatically metabolized. Consequently, both hepatic and renal dysfunctions have the potential to inhibit the elimination of amphetamine and result in prolonged exposures.

### Drug Interaction Studies

#### *CYP Enzymes*

*In vitro* experiments with human microsomes indicate minor inhibition of CYP2D6 by amphetamine and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites. However, because of the probability of auto-inhibition and the lack of information on the concentration of these metabolites relative to *in vivo* concentrations, no predications regarding the potential for amphetamine or its metabolites to inhibit the metabolism of other drugs by CYP isozymes *in vivo* can be made.

#### *Urine pH Modulators*

Because amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates. Alkaline urine pH results in less ionization and reduced renal elimination; acidic pH and high flow rates result in increased renal elimination with clearances greater than glomerular filtration rates, indicating the involvement of active secretion. In addition, any decrease in amphetamine's metabolism that might occur due to drug interactions or genetic polymorphisms is more likely to be clinically significant when renal elimination is decreased [see [Drug Interactions \(7.1\)](#)].

#### *Alcohol Effect*

There is no *in vivo* study conducted for the effect of alcohol on drug exposure. An *in vitro* dissolution study on DYANAVEL XR extended-release oral suspension showed alcohol-induced dose dumping potential in the presence of 40% alcohol. A similar study on the DYANAVEL XR extended-release tablets

showed no alcohol-induced dose dumping in the presence of 40% alcohol. Dose dumping was not observed in the presence of 5%, 10%, or 20% alcohol concentrations for either product.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

##### Carcinogenesis

No evidence of carcinogenicity was found in studies in which *d, l*-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 7, 5, and 2 times, respectively, the maximum recommended human dose of 20- mg/day (as base equivalents) given to adults, on a mg/m<sup>2</sup> basis.

##### Mutagenesis

Amphetamine, in the enantiomer ratio (*d*- to *l*- ratio of approximately 3:1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test *in vitro*. *d, l*-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

##### Impairment of Fertility

Amphetamine, in the enantiomer ratio (*d*- to *l*- ratio of approximately 3:1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day [approximately 10 times the maximum recommended human dose of 20 mg/day (as base equivalents) given to adults on a mg/m<sup>2</sup> basis].

#### 13.2 Animal Toxicology and/or Pharmacology

Acute administration of high doses of amphetamine (*d*- or *d, l*-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage, in rodents. The significance of these findings to humans is unknown.

### 14 CLINICAL STUDIES

The efficacy of DYANAVEL XR extended-release oral suspension was evaluated in a laboratory classroom study conducted in 108 pediatric patients (aged 6 to 12 years) with ADHD. The study began with an open-label dose optimization period (5 weeks) with an initial DYANAVEL XR dose of 2.5 or 5 mg once daily in the morning. The dose could be titrated weekly in increments of 2.5 to 10 mg until an optimal dose or the maximum dose of 20 mg/day was reached. Subjects then entered a 1-week randomized, double-blind treatment with the individually optimized dose of DYANAVEL XR or placebo. At the end of the week, school teachers and raters evaluated the attention and behavior of the subjects in a laboratory classroom using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale. SKAMP is a 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting. Each item is rated on a 7-point impairment scale.

The primary efficacy endpoint was change from pre-dose in the SKAMP-Combined score at 4 hours post-dosing. The key secondary efficacy parameters were onset and duration of clinical effect. The change scores from pre-dose 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 parameters. Results from the double-blind, placebo-controlled week of the study are summarized in Table 3 and Figure 3.

SKAMP-Combined change scores from pre-dose demonstrated a statistically significant improvement at all time points (1, 2, 4, 6, 8, 10, 12, 13 hours) post-dosing with DYANAVEL XR compared to placebo.

**Table 3. Summary of Primary Efficacy Results in Pediatric Patients (6 to 12 years) with ADHD**

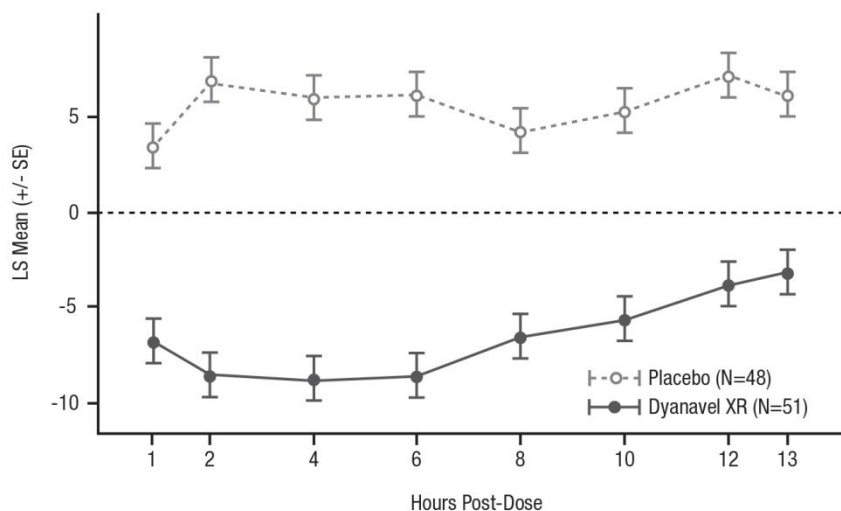
Study Number	Treatment Group	Primary Efficacy Measure: SKAMP-Combined Score
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		Mean Pre-dose Score (SD)	LS Mean Change from Pre-Dose at 4 Hours Post-Dosing (SE)	Placebo-subtracted Difference <sup>a</sup> (95% CI)
Study 1	DYANAVEL XR Extended-Release Oral Suspension	17.3 (8.88)	-8.8 (1.14)	-14.8 (-17.9, -11.6)
	Placebo	15.5 (7.35)	6.0 (1.19)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

<sup>a</sup> Difference (drug minus placebo) in least-squares mean change from pre-dose.

**Figure 3. LS Mean Change from Pre-dose in SKAMP-Combined Score after Treatment with DYANAVEL XR Extended-Release Oral Suspension or Placebo in Pediatric Patients (6 to 12 years) with ADHD**



## 16 HOW SUPPLIED/STORAGE AND HANDLING

### How Supplied

DYANAVEL XR (amphetamine) extended-release oral suspension: The concentration is 2.5 mg/mL amphetamine base equivalents and is supplied as light beige to tan viscous suspension with bubblegum flavor in bottles of 464 mL (NDC 24478-102-01).

The product is provided in a carton. Each carton also contains four oral dispensers and four bottle adapters.

DYANAVEL XR (amphetamine) extended-release tablets: Supplied in bottles (that contain a desiccant) with child-resistant closure as 5 mg, 10 mg, 15 mg, and 20 mg strengths.

- 5 mg DYANAVEL XR extended-release tablet is functionally scored and is available as an off-white, speckled, caplet shaped tablet with 5 debossed on one side and scored on the other side, supplied in bottles of 30 (NDC 24478-106-01).
- 10 mg DYANAVEL XR extended-release tablet is available as an off-white, speckled, diamond shaped tablet with 10 debossed on one side and plain on the other side, supplied in bottles of 30 (NDC 24478-108-01).



- 15 mg DYANAVEL XR extended-release tablet is available as an off-white, speckled, triangle shaped tablet with 15 debossed on one side and plain on the other side, supplied in bottles of 30 (NDC 24478-109-01).
- 20 mg DYANAVEL XR extended-release tablet is available as an off-white, speckled, oval shaped tablet with 20 debossed on one side and plain on the other side, supplied in bottles of 30 (NDC 24478-110-01).

### **Storage and Handling**

Dispense in a tight container with child-resistant closure.

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

DYANAVEL XR extended-release oral suspension: The pharmacist should insert the bottle adapter firmly into the neck of the bottle and provide the oral dosing dispenser to the patient when dispensing this product.

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling ([Medication Guide](#) and [Instructions for Use](#)).

### Abuse, Misuse, and Addiction

Educate patients and their families about the risks of abuse, misuse, and addiction of DYANAVEL XR, which can lead to overdose and death, and proper disposal of any unused drug [see [Warnings and Precautions \(5.1\)](#), [Drug Abuse and Dependence \(9.2\)](#), [Overdosage \(10\)](#)]. Advise patients to store DYANAVEL XR in a safe place, preferably locked, and instruct patients to not give DYANAVEL XR to anyone else.

### Dosage and Administration Instructions

Provide the following instructions on administration to the patient [see [Dosage and Administration \(2.3\)](#)]:

#### *DYANAVEL XR extended-release oral suspension*

- Use with the oral dosing dispenser provided by the pharmacist.
- Ensure that the bottle adapter has been firmly inserted into the bottle by the pharmacist. Do not remove the bottle adapter once it has been inserted into the bottle.
- Shake the bottle before each dose.

#### *DYANAVEL XR extended-release tablets*

- Tablets may be chewed or swallowed whole.

### Risks to Patients with Serious Cardiac Disease

Advise patients that there are potential risks to patients with serious cardiac disease, including sudden death, with DYANAVEL XR use. Instruct patients to contact a healthcare provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease [see [Warnings and Precautions \(5.2\)](#)].

### Increased Blood Pressure and Heart Rate

Instruct patients and their caregivers that DYANAVEL XR can cause elevations of their blood pressure and pulse rate [see [Warnings and Precautions \(5.3\)](#)].

### Psychiatric Adverse Reactions

Advise patients and their caregivers that DYANAVEL XR, at recommended doses, may cause psychotic or manic symptoms, even in patients without a prior history of psychotic symptoms or mania [see [Warnings and Precautions \(5.4\)](#)].

### Long-Term Suppression of Growth in Pediatric Patients

Advise patients and their caregivers that DYANAVEL XR may cause slowing of growth and weight loss [see [Warnings and Precautions \(5.5\)](#)].

#### Circulation Problems in Fingers and Toes /Peripheral vasculopathy, including Raynaud's phenomenon/

Instruct patients and their caregivers beginning treatment with DYANAVEL XR 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 and their caregivers to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes.

Instruct patients and their caregivers to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking DYANAVEL XR.

Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients [see [Warnings and Precautions \(5.6\)](#)].

#### Serotonin Syndrome

Caution patients and their caregivers about the risk of serotonin syndrome with concomitant use of DYANAVEL XR and other serotonergic drugs including SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort, and with drugs that impair metabolism of serotonin (in particular MAOIs, both those intended to treat psychiatric disorders and also others such as linezolid [see [Contraindications \(4\)](#), [Warnings and Precautions \(5.7\)](#) and [Drug Interactions \(7.1\)](#)].

Advise patients to contact their healthcare provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome.

#### Motor and Verbal Tics, and Worsening of Tourette's Syndrome

Advise patients that motor and verbal tics and worsening of Tourette's Syndrome may occur during treatment with DYANAVEL XR. Instruct patients to notify their healthcare provider if emergence of new tics or worsening of tics or Tourette's syndrome occurs [see [Warnings and Precautions \(5.8\)](#)].

#### Concomitant Medications

Advise patients and their caregivers to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs because there is a potential for interactions [see [Drug Interactions \(7.1\)](#)].

#### Pregnancy Registry

Advise patients and their caregivers that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DYANAVEL XR during pregnancy [see [Use in Specific Populations \(8.1\)](#)].

#### Pregnancy

Advise patients and their caregivers to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with DYANAVEL XR. Advise patients of the potential fetal effects from the use of DYANAVEL XR during pregnancy [see [Use in Specific Populations \(8.1\)](#)].

#### Lactation

Advise women not to breastfeed if they are taking DYANAVEL XR [see [Use in Specific Populations \(8.2\)](#)].

#### Alcohol

Advise patients to avoid alcohol while taking DYANAVEL XR. Consumption of alcohol while taking DYANAVEL XR may result in a more rapid release of the dose of amphetamine [see [Clinical Pharmacology \(12.3\)](#)].

Manufactured by:

**Tris Pharma, Inc.**

Monmouth Junction, NJ 08852

LB8684  
Rev. 01

## MEDICATION GUIDE

**DYANAVEL® XR (dī-an-uh-vel)  
(amphetamine) extended-release oral suspension, CII**

**DYANAVEL® XR (dī-an-uh-vel)  
(amphetamine) extended-release tablets, CII**

### **What is the most important information I should know about DYANAVEL XR?**

#### **DYANAVEL XR may cause serious side effects, including:**

- **Abuse, misuse, and addiction.** DYANAVEL XR has a high chance for abuse and misuse and may lead to substance use problems, including addiction. Misuse and abuse of DYANAVEL XR, other amphetamine containing medicines, and methylphenidate containing medicines, can lead to overdose and death. The risk of overdose and death is increased with higher doses of DYANAVEL XR or when it is used in ways that are not approved, such as snorting or injection.
  - Your healthcare provider should check you or your child's risk for abuse, misuse, and addiction before starting, treatment with DYANAVEL XR and will monitor you or your child during treatment
  - DYANAVEL XR may lead to physical dependence after prolonged use, even if taken as directed by your healthcare provider.
  - Do not give DYANAVEL XR to anyone else. See **"What is DYANAVEL XR?"** for more information.
  - Keep DYANAVEL XR in a safe place and properly dispose of any unused medicine. See **"How should I store DYANAVEL XR?"** for more information. Tell your healthcare provider if you or your child have ever abused or been dependent on alcohol, prescription medicines, or street drugs.

- **Risks for people with serious heart disease.** Sudden death has happened in people who have heart defects or other serious heart disease. Your healthcare provider should check you or your child carefully for heart problems before starting treatment with DYANAVEL XR. Tell your healthcare provider if you or your child have any heart problems, heart disease, or heart defects.

**Call your healthcare provider or go to the nearest hospital emergency room right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting during treatment with DYANAVEL XR.**

- **Increased blood pressure and heart rate.** Your healthcare provider should check you or your child's blood pressure and heart rate regularly during treatment with DYANAVEL XR.
- **Mental (psychiatric) problems, including:**
  - new or worse behavior and thought problems
  - new or worse bipolar illness
  - new psychotic symptoms (such as hearing voices, or seeing or believing things that are not real) or new manic symptoms

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

**Call your healthcare provider right away if you or your child have any new or worsening mental symptoms or problems during treatment with DYANAVEL XR, especially hearing voices, seeing or believing things that are not real, or new manic symptoms.**

### **What is DYANAVEL XR?**

DYANAVEL XR is a central nervous system (CNS) stimulant prescription medicine used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in people 6 years of age and older.

DYANAVEL XR may help increase attention and decrease impulsiveness and hyperactivity in people with ADHD.

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

**DYANAVEL XR is a federally controlled substance (CII) because it contains amphetamine that can be a target for people who abuse prescription medicines or street drugs.** Keep DYANAVEL XR in a safe place to protect it from theft. Never give your DYANAVEL XR to anyone else, because it may cause death or harm them. Selling or giving away DYANAVEL XR may harm others and is against the law.

**Do not take DYANAVEL XR if you or your child are:**

- allergic to amphetamine products or any of the ingredients in DYANAVEL XR. See the end of this Medication Guide for a complete list of ingredients in DYANAVEL XR.
- taking, or have taken within the past 14 days a medicine called a monoamine oxidase inhibitor (MAOI), including the antibiotic linezolid and the intravenous medicine methylene blue. Ask your healthcare provider or pharmacist if you are not sure if you or your child take any of these medicines.

**Before taking DYANAVEL XR tell your healthcare provider about all medical conditions, including if you or your child:**

- have heart problems, heart disease, heart defects, or high blood pressure
- have mental problems including psychosis, mania, bipolar illness, or depression
- have circulation problems in fingers and toes
- have or had repeated movements or sounds (tics) or Tourette's syndrome, or have a family history of tics or Tourette's syndrome
- are pregnant or plan to become pregnant. It is not known if DYANAVEL XR will harm the unborn baby.
  - There is a pregnancy registry for females who are exposed to DYANAVEL XR during pregnancy. The purpose of the registry is to collect information about the health of females exposed to DYANAVEL XR and their baby. If you or your child becomes pregnant during treatment with DYANAVEL XR, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychostimulants at 1-866-961-2388.
- are breastfeeding or plan to breastfeed. DYANAVEL XR passes into breast milk. You or your child should not breastfeed during treatment with DYANAVEL XR.

**Tell your healthcare provider about all of the medicines that you or your child takes,** including prescription and over-the-counter medicines, vitamins, and herbal supplements.

DYANAVEL XR and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted during treatment with DYANAVEL XR.

**Especially tell your healthcare provider if you or your child take:**

- |                                                        |                                                              |
|--------------------------------------------------------|--------------------------------------------------------------|
| • MAOIs                                                | • selective serotonin reuptake inhibitors (SSRIs)            |
| • serotonin norepinephrine reuptake inhibitors (SNRIs) | • medicines used to treat migraine headaches called triptans |
|                                                        | • fentanyl                                                   |
| • tricyclic antidepressants                            | • tramadol                                                   |
| • lithium                                              | • buspirone                                                  |
| • tryptophan                                           | • St. John's Wort                                            |

Your healthcare provider will decide whether DYANAVEL XR can be taken with other medicines.

**Do not start any new medicine during treatment with DYANAVEL XR without talking to your healthcare provider first.**

**How should I take DYANAVEL XR?**

- **See the detailed “Instructions for Use” for information on how to give a dose of DYANAVEL XR extended-release oral suspension.**

- Take DYANAVEL XR exactly as prescribed by your healthcare provider.
- Your healthcare provider may change the dose if needed.
- Take DYANAVEL XR 1 time each day in the morning.
- DYANAVEL XR can be taken with or without food.
- DYANAVEL XR extended-release tablets may be chewed or swallowed whole.
- DYANAVEL XR extended-release 5 mg tablets are scored and can be divided into equal parts at the score line.

If you or your child take too much DYANAVEL XR, call your healthcare provider or Poison Help line at 1-800-222-1222, or go to the nearest hospital emergency room right away.

**What should I avoid during treatment with DYANAVEL XR?**

You should avoid drinking alcohol during treatment with DYANAVEL XR.

**What are possible side effects of DYANAVEL XR?**

**DYANAVEL XR may cause serious side effects, including:**

- See **“What is the most important information I should know about DYANAVEL XR?”**
- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with DYANAVEL XR. Your healthcare provider may stop your child’s DYANAVEL XR treatment if they are not growing or gaining weight as expected.
- **Circulation problems in fingers and toes (peripheral vasculopathy, including Raynaud’s phenomenon).** Signs and symptoms may include:
  - fingers or toes may feel numb, cool, painful
  - fingers or toes may change color from pale, to blue, to red

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

**Call your healthcare provider right away if you or your child have any signs of unexplained wounds appearing on fingers or toes during treatment with DYANAVEL XR.**

- **New or worsening tics or worsening Tourette’s syndrome.** Tell your healthcare provider if you or your child get any new or worsening tics or worsening Tourette’s syndrome during treatment with DYANAVEL XR.
- **Serotonin Syndrome.** This problem may happen when DYANAVEL XR is taken with certain other medicines and may be life-threatening. Stop taking DYANAVEL XR and call your healthcare provider or go to the nearest hospital emergency room if you get symptoms of serotonin syndrome which may include:
 

○ agitation	○ confusion
○ fast heart beat	○ dizziness
○ flushing	○ tremors, stiff muscles, or muscle twitching
○ seizures	○ seeing or hearing things that are not real (hallucination)
○ coma	○ changes in blood pressure
○ sweating	○ high body temperature (hyperthermia)
○ loss of coordination	○ nausea, vomiting, diarrhea

**The most common side effects of DYANAVEL XR include:**

- |                      |                    |                        |
|----------------------|--------------------|------------------------|
| • dry mouth          | • nausea           | • extreme mood changes |
| • decreased appetite | • trouble sleeping | • dizziness            |
| • weight loss        | • restlessness     | • increased heart rate |
| • stomach pain       |                    |                        |

These are not all of the possible side effects of DYANAVEL XR.

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

**How should I store DYANAVEL XR?**

- Store DYANAVEL XR at room temperature between 68°F to 77°F (20°C to 25°C).
- Store DYANAVEL XR in a safe place, like a locked cabinet.
- Dispose of remaining, unused, or expired DYANAVEL XR by a medicine take-back program at a U.S. Drug Enforcement Administration (DEA) authorized collection site. If no take-back program or DEA authorized collector is available, mix DYANAVEL XR with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away DYANAVEL XR in the household trash. Visit [www.fda.gov/drugdisposal](http://www.fda.gov/drugdisposal) for additional information on disposal of unused medicines.

**Keep DYANAVEL XR and all medicines out of the reach of children.**

**General information about the safe and effective use of DYANAVEL XR.**

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not use DYANAVEL XR for a condition for which it has not been prescribed. Do not give DYANAVEL XR to other people, even if they have the same symptoms. It may harm them and it is against the law. You can ask your healthcare provider or pharmacist for information about DYANAVEL XR that is written for healthcare professionals.

**What are the ingredients in DYANAVEL XR?**

**DYANAVEL XR extended-release oral suspension:**

**Active Ingredients:** amphetamine, dextroamphetamine sulfate and amphetamine aspartate.

**Inactive Ingredients:** anhydrous citric acid, bubblegum flavor, glycerin, methylparaben, modified starch, polysorbate 80, povidone, polyvinyl acetate, propylparaben, sodium lauryl sulfate, sodium polystyrene sulfonate, sucralose, triacetin and xanthan gum.

**DYANAVEL XR extended-release tablets:**

**Active Ingredients:** amphetamine, dextroamphetamine sulfate and amphetamine aspartate.

**Inactive Ingredients:** bubblegum flavor, crospovidone, guar gum, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl acetate, povidone, silicon dioxide, sodium polystyrene sulfonate, sucralose, talc, triacetin and xanthan gum.

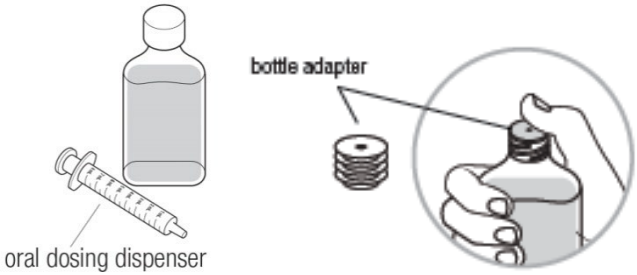


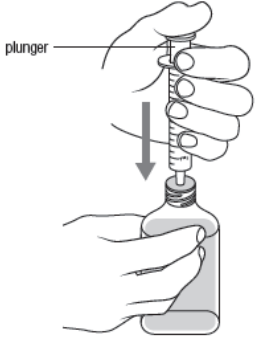
Manufactured by: Tris Pharma, Inc., Monmouth Junction, NJ 08852

For more information about DYANAVEL XR go to [www.dyanavelxr.com](http://www.dyanavelxr.com) or call 1-732-940-0358.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 10/2023

**Instructions for Use**  
**DYANAVEL® XR (dī-an-uh-vel)**  
**(amphetamine)**  
**extended-release oral suspension, CII**

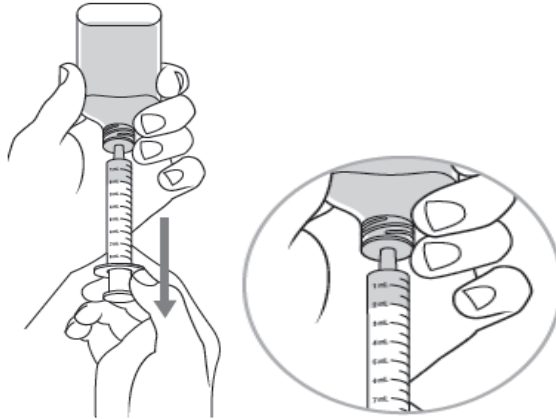
Read this Instructions for Use before taking DYANAVEL XR and each time you get a refill. There may be new information. This leaflet does not take the place of talking with the healthcare provider about your or your child's medical condition or treatment.

<p><b>Step 1:</b></p> <ul style="list-style-type: none"><li>• Check the DYANAVEL XR bottle to make sure that the bottle adapter has been inserted into the bottle by the pharmacist. <b>Do not remove the bottle adapter.</b></li><li>• Check to make sure your pharmacist has given you an oral dosing dispenser.</li><li>• Tell your pharmacist if an oral dosing dispenser is not provided or the bottle adapter is missing from the neck of the bottle.</li></ul>	 <p>The diagram illustrates the components for Step 1: a bottle of DYANAVEL XR, an oral dosing dispenser, and a bottle adapter. A circular inset shows a hand holding the bottle with the adapter inserted into the neck.</p>
<p><b>Step 2:</b></p> <ul style="list-style-type: none"><li>• Shake the bottle well (up and down).</li></ul>	 <p>The diagram shows a hand shaking the bottle up and down, indicated by a vertical double-headed arrow.</p>
<p><b>Step 3:</b></p> <ul style="list-style-type: none"><li>• Check the DYANAVEL XR oral dosing dispenser to find the right dose in milliliters (mL) that you or your child's healthcare provider has prescribed.</li></ul>	 <p>The diagram shows a close-up of the oral dosing dispenser with markings for 1 mL, 2 mL, 3 mL, and 4 mL.</p>
<p><b>Step 4:</b></p> <ul style="list-style-type: none"><li>• Place the DYANAVEL XR bottle upright and insert tip of the oral dosing dispenser into the bottle.</li></ul> <p><b>Step 5:</b></p> <ul style="list-style-type: none"><li>• Push the plunger all the way down.</li></ul>	 <p>The diagram shows a hand inserting the oral dosing dispenser into the bottle and pushing the plunger down, indicated by a downward arrow.</p>



**Step 6:**

- With the oral dosing dispenser in place, hold the DYANAVEL XR bottle with 1 hand and turn the bottle upside down. Pull the plunger down until the white end of the plunger reaches the number of mLs you need for the prescribed dose.



**Step 7:**

- Turn the bottle over and place upright on a counter top, then remove the oral dosing dispenser from the bottle adapter.



**Step 8:**

- Place the tip of the oral dosing dispenser into you or your child's mouth. Point the tip toward the cheek and slowly push the plunger all the way down to give the DYANAVEL XR dose.



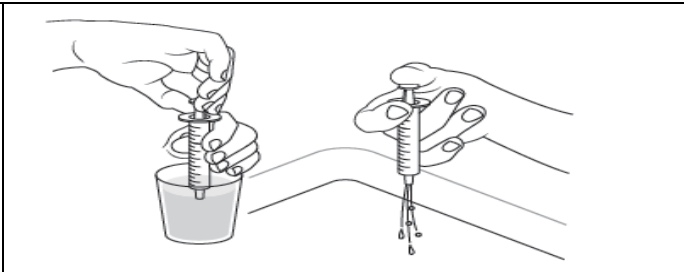
**Step 9:**

- Put the DYANAVEL XR cap back on the bottle and close tightly.



**Step 10:**

- Clean the oral dosing dispenser after each use by placing in the dishwasher, or by rinsing with tap water.

**How should I store DYANAVEL XR?**

- Store DYANAVEL XR at room temperature between 68°F to 77°F (20°C to 25°C).
- Store DYANAVEL XR in a safe place, like a locked cabinet.
- Dispose of remaining, unused, or expired DYANAVEL XR by a medicine take-back program at a U.S. Drug Enforcement Administration (DEA) authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or DEA authorized collector is available, mix DYANAVEL XR with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away DYANAVEL XR in the household trash.

**Keep DYANAVEL XR and all medicines out of the reach of children.**

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