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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

Indications and Usage (1)	09/2025
Warnings and Precautions (5.7)	09/2025

INDICATIONS AND USAGE

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

Limitations of Use

The use of QUILLIVANT XR is not recommended in pediatric patients younger than 6 years of age because they had higher plasma exposure and a higher incidence of adverse reactions (e.g., weight loss) than patients 6 years and older at the same dosage (5.7, 8.4).

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 (≥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.

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: 09/2025

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FULL PRESCRIBING INFORMATION: CONTENTS*

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

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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)]*.

Limitations of Use

The use of QUILLIVANT XR is not recommended in pediatric patients younger than 6 years of age because they had higher plasma exposure and a higher incidence of adverse reactions (e.g., weight loss) than patients 6 years and older at the same dosage *[see Warnings and Precautions (5.7), Use in Specific Populations (8.4)]*.

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.

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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 25ºC (77ºF); excursions permitted from 15º to 30ºC (59º to 86ºF). 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.

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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.

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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.

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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

QUILLIVANT XR is not approved for use and is not recommended in pediatric patients below 6 years of age *[see Use in Specific Populations (8.4)]*.

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)]*

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- 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 (≥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 (≥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.

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Table 2: Common Adverse Reactions occurring in ≥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, 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

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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

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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^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Limited published literature reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. Long-term neurodevelopmental effects on infants from CNS stimulant exposure are unknown. The developmental and health benefits of

breastfeeding should be considered along with the mother's clinical need for 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 not been established in pediatric patients below the age of 6 years.

In studies evaluating extended-release methylphenidate products, patients 4 to <6 years of age had higher systemic methylphenidate exposures than those observed in older pediatric patients at the same dosage. Pediatric patients 4 to <6 years of age also had a higher incidence of adverse reactions, including weight loss.

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 old's 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.

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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^2 basis.

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

8.5 Geriatric Use

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

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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.

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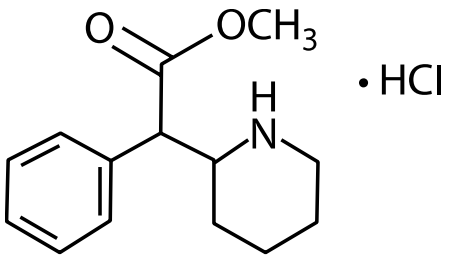
Methylphenidate HCl is a central nervous system (CNS) stimulant. The chemical name is methyl α-phenyl-2-piperidineacetate hydrochloride, and its structural formula is shown in Figure 1.

Figure 1: Methylphenidate HCl structure



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

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

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 (± SD) peak plasma concentrations of 13.6 (± 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%.

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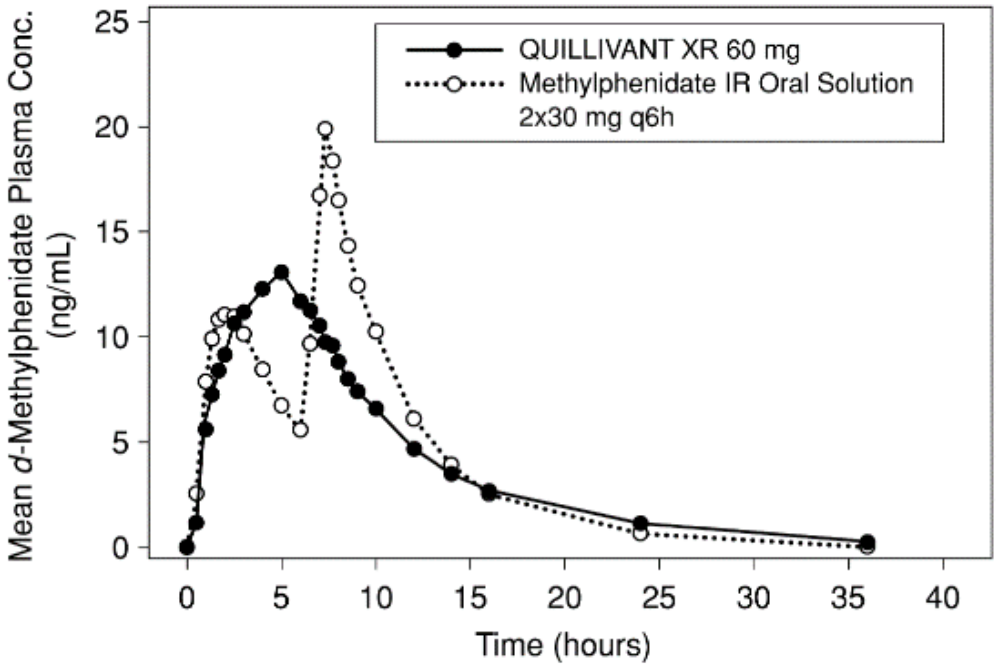
Figure 2: Mean *d*-Methylphenidate Plasma Concentration-Time Profiles



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 ±SD) after 60 mg oral dosing of QUILLIVANT XR*

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

* Breakfast was given 30 min prior to drug administration

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

‡ data presented as median (range)

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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 (± 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.

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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^2 basis. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

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

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

The efficacy of 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

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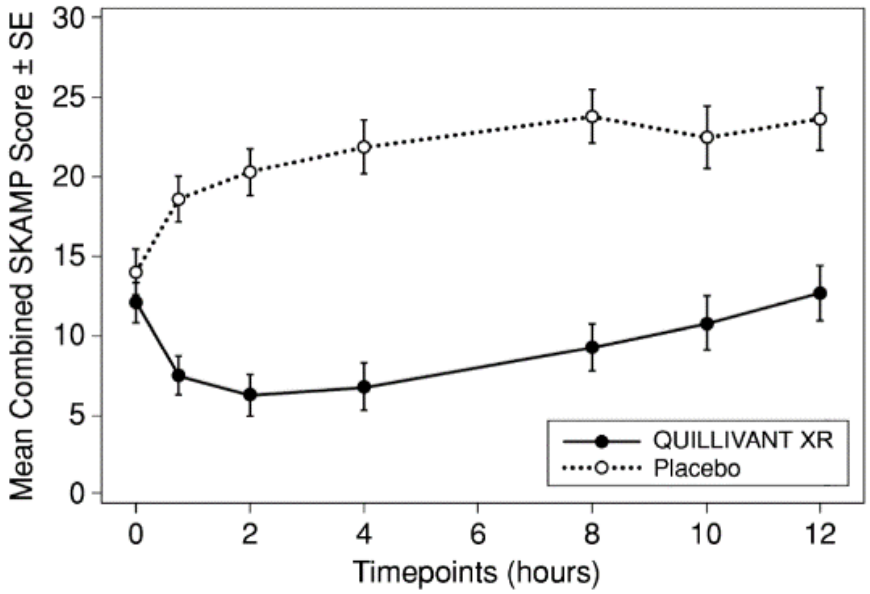
began with an open-label dose optimization period (4 to 6 weeks) with an initial QUILLIVANT XR dose of 20 mg once daily in the morning. The dose could be titrated weekly in increments of 10 or 20 mg until a therapeutic dose or the maximum dose of 60 mg/day was reached. At the end of the dose optimization 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.

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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 25ºC (77ºF); excursions permitted from 15ºC to 30ºC (59ºF to 86ºF). [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.

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- 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)]*.

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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

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

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

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Rev. 03

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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

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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.

QUILLIVANT XR is not recommended for use in children under 6 years of age with ADHD.

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).

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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.**

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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:

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- 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.**

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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.
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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 or call (732) 940-0358.
This product's label may have been updated. For current full prescribing information, please visit www.trispharma.com.

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

Revised: 09/2025

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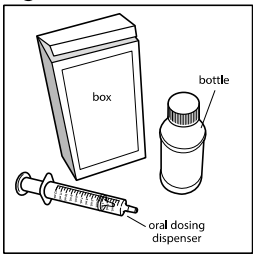
Instructions for Use

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.

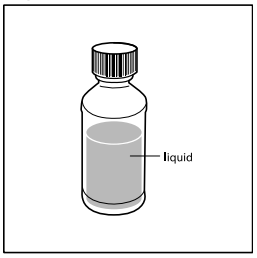
Step 1. Remove the QUILLIVANT XR bottle and oral dosing dispenser from the box **(See Figure A).** If the oral dosing dispenser is missing or not provided, please contact your pharmacist for a replacement.

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).**

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Figure C

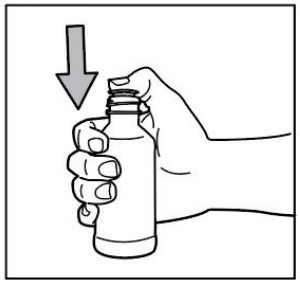
Step 4. Uncap the bottle and check that the bottle adapter has been fully inserted into the bottle **(See Figure D).**

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.

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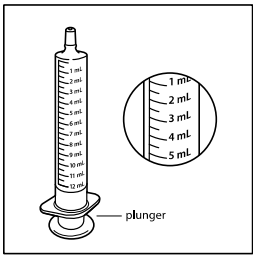
Figure G

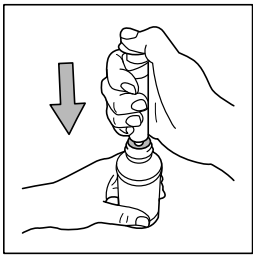
Step 5. Check the QUILLIVANT XR dose in milliliters (mL) as prescribed by your health care provider. Locate this number on the oral dosing dispenser **(See Figure H).**

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**).

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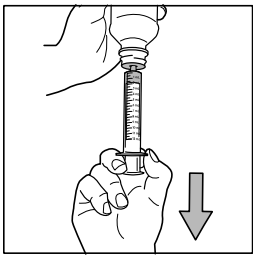
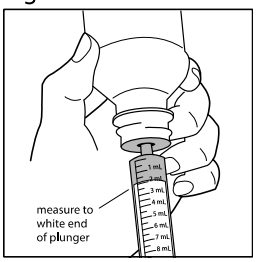
Figure J



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).**

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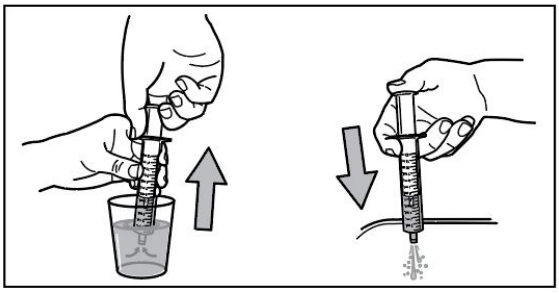
Figure M

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.

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Monmouth Junction, NJ 08852

LB8529 Rev. 01 06/2021

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

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

WARNING: ABUSE, 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 (≥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*.

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: CONTENTS*

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

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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.

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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

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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).

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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.

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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)]*

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- 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 (≥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 (≥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.

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

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

6.2 Postmarketing Experience

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

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

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

Eye Disorders: Diplopia, 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

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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

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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^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m^2 basis).

8.2 Lactation

Risk Summary

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

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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 mg/m^2 basis.

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

8.5 Geriatric Use

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

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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).

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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.

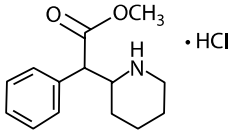
11 DESCRIPTION

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

Figure 1: Methylphenidate HCl structure



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

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

QuilliChew ER also contains the following inactive ingredients: aspartame *[see Warnings and Precautions (5.8)]*, cherry flavor, citric acid, crospovidone, D&C red #30 (for 30 mg strength), D&C red #7 (for 40 mg strength), guar gum, magnesium stearate, mannitol, microcrystalline

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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

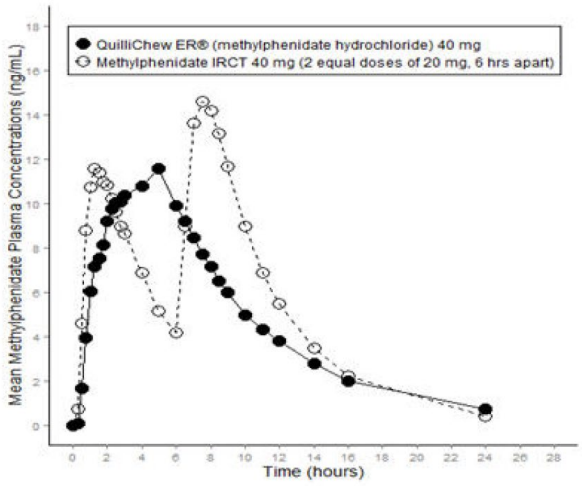
Methylphenidate is a racemic mixture comprised of the *d*- and *l*-isomers. The *d*-isomer is more pharmacologically active than the *l*-isomer. The mode of therapeutic action in ADHD is not known. Methylphenidate blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increases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

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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.

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

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

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

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

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

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

Table 2: Primary Efficacy Result (ITT Population)

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

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

[a]Least-Squares Mean Difference (drug minus placebo).

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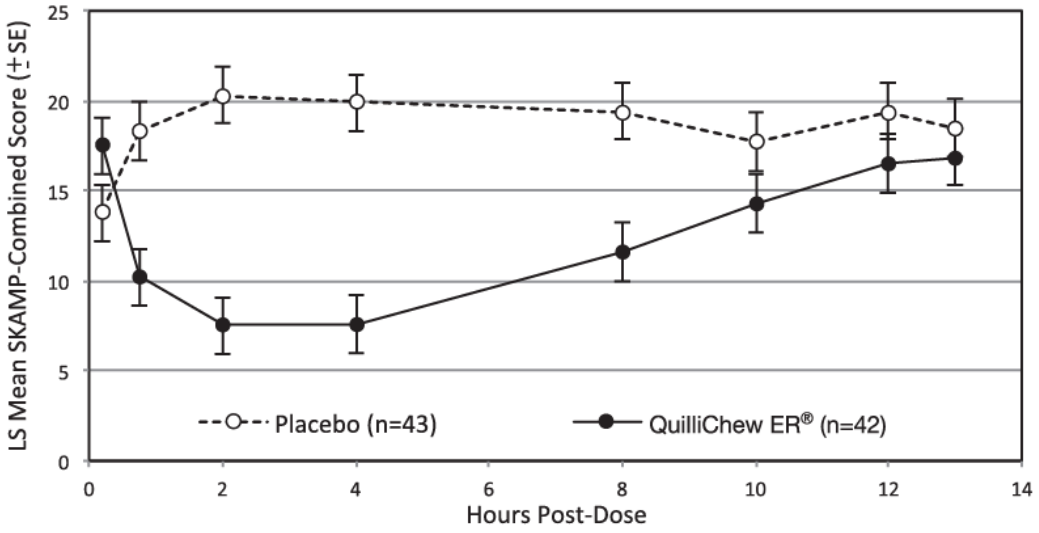
Figure 3: SKAMP-Combined Scores Over Time (LS Mean ±SE) by Treatment Group (ITT Population)



ITT: intent-to-treat

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

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

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

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

The product is supplied in bottles of 100.

QuilliChew ER extended-release chewable tablets			
Package Configuration	Tablet Strength (mg)	NDC	Print

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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 20ºC to 25ºC (68ºF to 77ºF); excursions permitted from 15ºC to 30ºC (59ºF to 86ºF). [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]

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- 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.

Distributed by:

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

Manufactured by:

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LB8533

Rev.02

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MEDICATION GUIDE
QuilliChew ER®(quil-ih' CHOO' ee-ahr)

(methylphenidate hydrochloride)

extended-release chewable tablets CII

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

QuilliChew ER 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

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- 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.

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- 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.

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- 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.

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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:**
  - o fingers or toes may feel numb, cool, painful
  - o 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 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:

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

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

Call your 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

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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 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.

This product's label may have been updated. For current full prescribing information, please visit www.trispharma.com.

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

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DYANAVEL®XR safely and effectively. See full prescribing information for DYANAVEL XR.

DYANAVEL®XR (amphetamine) extended-release oral suspension, CII
DYANAVEL® 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.

----------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.

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FULL PRESCRIBING INFORMATION: CONTENTS*

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

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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-

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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.

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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)]*.

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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.

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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 (≥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 ≥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)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	3.8%	0%
Rhinitis allergic	3.8%	0%
Gastrointestinal disorders		
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

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7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Amphetamines

Table 2. Drugs having clinically important interactions with amphetamines.

MAO Inhibitors (MAOI)	
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 *Contraindications (4) and Warnings and Precautions (5.7)]*.
Serotonergic Drugs	
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 *Warnings and Precautions (5.7)]*.
CYP2D6 Inhibitors	
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 *Warnings and Precautions (5.7), Overdosage (10)]*.
Alkalinizing Agents (Urinary and Gastrointestinal)	
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.
Acidifying Agents (Urinary and Gastrointestinal)	
Clinical Impact	Lower blood levels and efficacy of amphetamines.
Intervention	Increase dose based on clinical response.
Tricyclic Antidepressants	

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Clinical Impact	May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of *d*-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^2 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^2 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^2 basis or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

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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.

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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:

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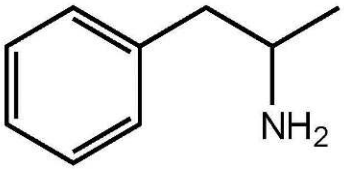

$C_9H_{13}N$ MW 135.21

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

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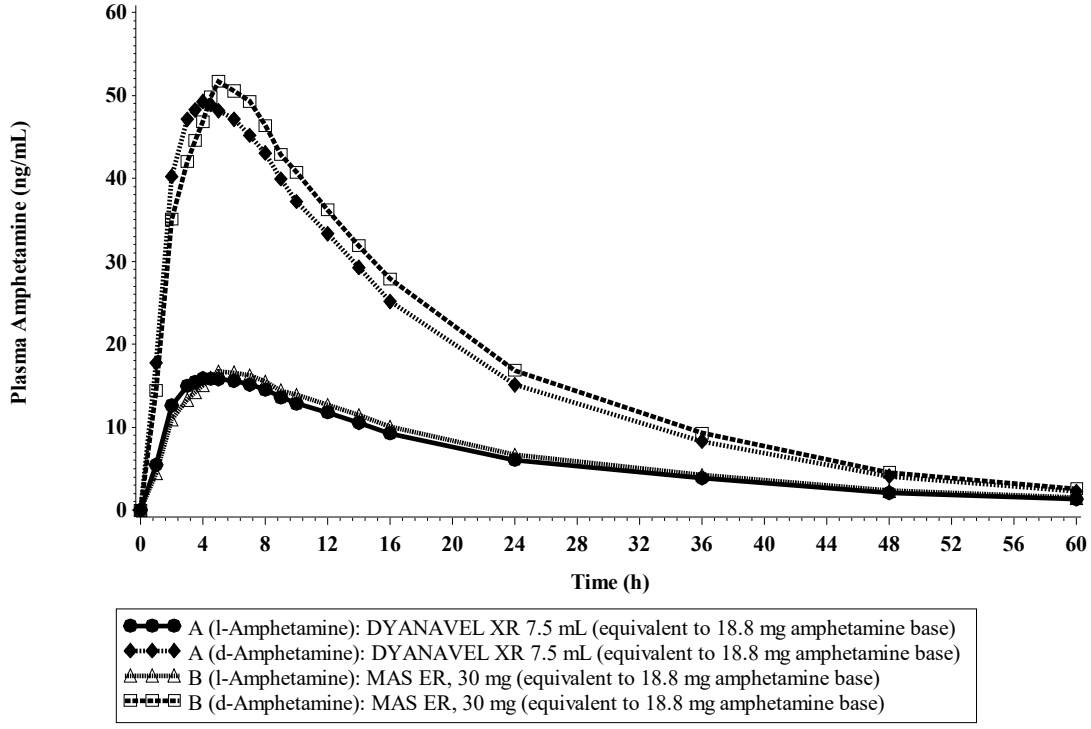
Absorption

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

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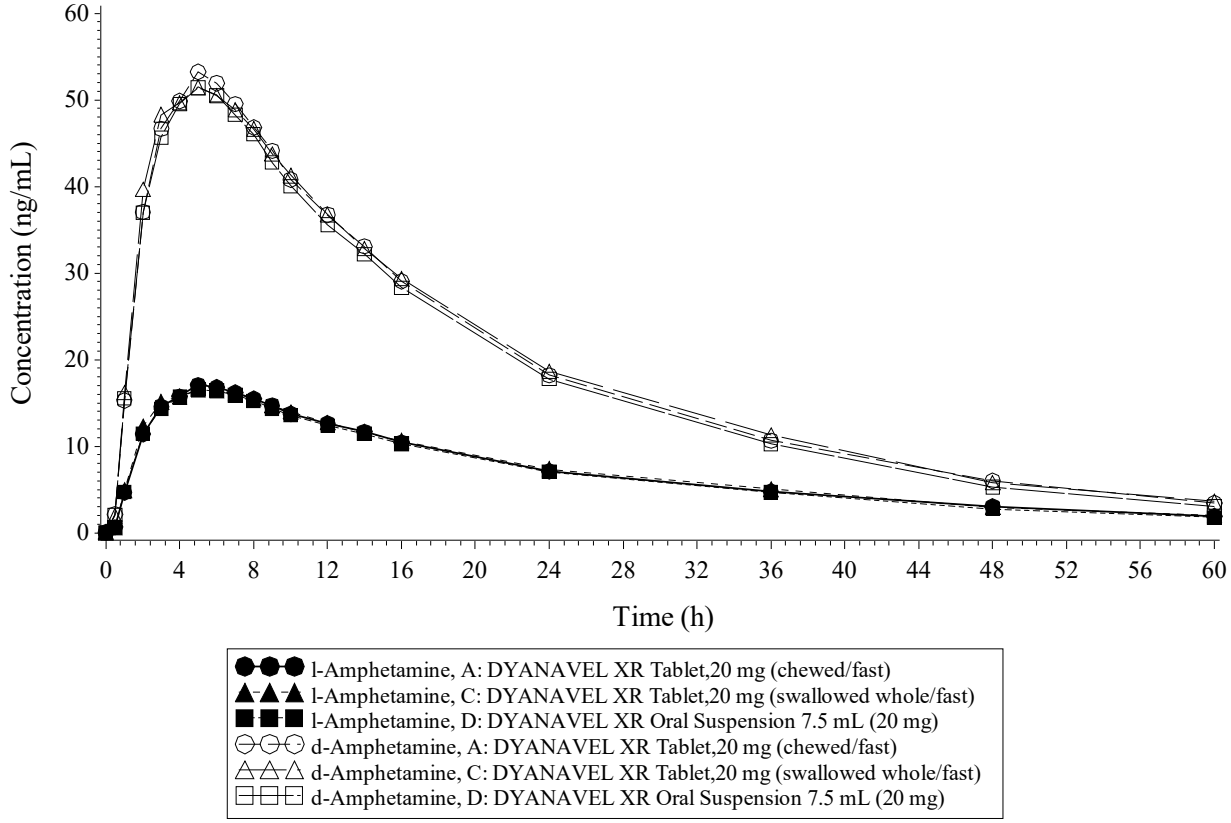
suspension. The relative bioavailability of DYANAVEL XR tablets compared with an equal dose of DYANAVEL XR oral suspension, for *d*- and *l*-amphetamine, were 105% and 106%, respectively.

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.

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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

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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^2 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^2 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.

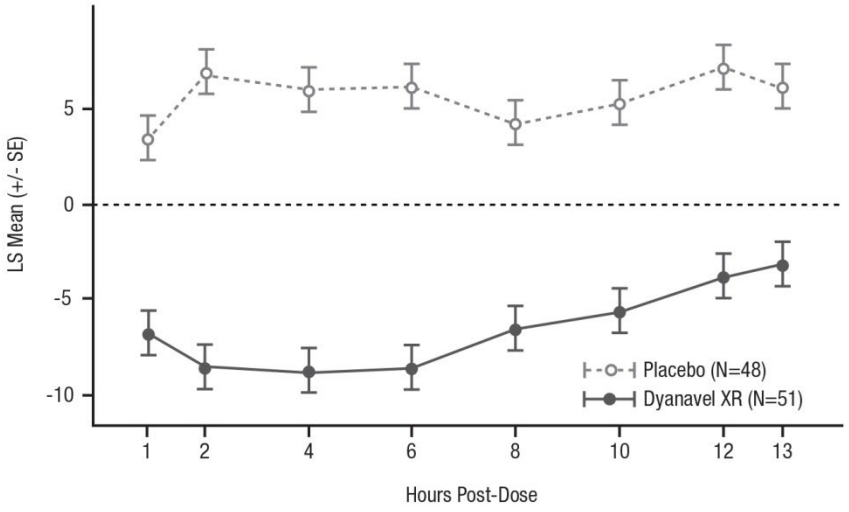
Table 3. Summary of Primary Efficacy Results in Pediatric Patients (6 to 12 years) with ADHD

Study Number	Treatment Group	Primary Efficacy Measure: SKAMP-Combined Score

		Mean Pre-dose Score (SD)	LS Mean Change from Pre-Dose at 4 Hours Post-Dosing (SE)	Placebo-subtracted Difference [a] (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.
[a] 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).

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- 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 15º to 30ºC (59º to 86ºF) *[*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

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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

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LB8684
Rev. 01

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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.

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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
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants
- lithium
- tryptophan
- selective serotonin reuptake inhibitors (SSRIs)
- medicines used to treat migraine headaches called triptans
- fentanyl
- tramadol
- buspirone
- 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?

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

The most common side effects of DYANAVEL XR include:

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

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

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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 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 or call 1-732-940-0358.

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

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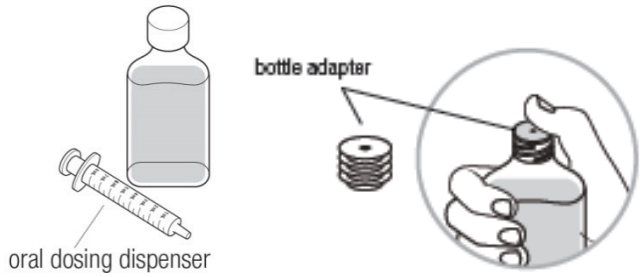
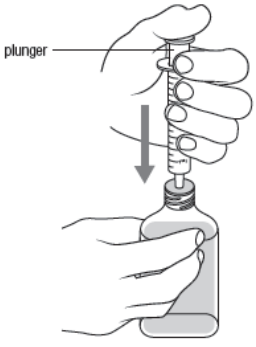
Instructions for Use
DYANAVEL® XR (dī-an-uh-vel)
(amphetamine)
extended-release oral suspension, CII

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.

Step 1: • Check the DYANAVEL XR bottle to make sure that the bottle adapter has been inserted into the bottle by the pharmacist. **Do not remove the bottle adapter**. • Check to make sure your pharmacist has given you an oral dosing dispenser. • Tell your pharmacist if an oral dosing dispenser is not provided or the bottle adapter is missing from the neck of the bottle.	
Step 2: • Shake the bottle well (up and down).	
Step 3: • 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.	
Step 4: • Place the DYANAVEL XR bottle upright and insert tip of the oral dosing dispenser into the bottle. **Step 5:** • Push the plunger all the way down.	

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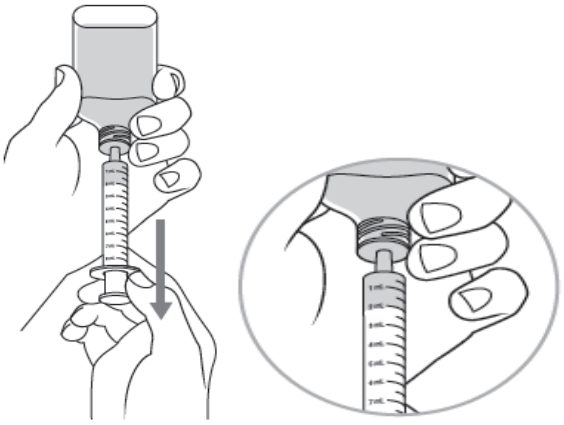
Step 6: • With the oral dosing dispenser in place, hold the DYANAVEL XR bottle with 1 hand and turn the bottle upside down. Pull the plunger down until the white end of the plunger reaches the number of mLs you need for the prescribed dose.	
Step 7: • Turn the bottle over and place upright on a counter 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.	

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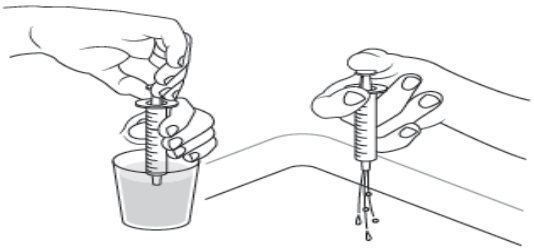
Step 10: • Clean the oral dosing dispenser after each use by placing in the dishwasher, or by rinsing with tap water.	

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.

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

For more information about DYANAVEL XR go to www.dyanavelxr.com or call 1-732-940-0358.

This Instructions for Use has been approved by the U.S. Food and Drug Administration

Revised: 10/2023

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ONYDA™ XR (clonidine hydrochloride) extended-release oral suspension
Initial U.S. Approval: 1974

RECENT MAJOR CHANGES

Warnings and Precautions (5.3) 04/2025

INDICATIONS AND USAGE

ONYDA XR is a centrally acting alpha$_2$-adrenergic agonist indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy or as adjunctive therapy to central nervous system (CNS) stimulant medications in pediatric patients 6 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- Starting dosage is 0.1 mg of ONYDA XR orally once daily at bedtime with or without food. Dosage may be increased in increments of 0.1 mg per day at weekly intervals. Maximum recommended dosage is 0.4 mg once daily at bedtime. (2.1)
- Do not substitute ONYDA XR for other clonidine products on a mg-per-mg basis because of differing pharmacokinetic profiles. (2.3)
- When discontinuing, taper the dose in decrements of no more than 0.1 mg every 3 to 7 days to avoid rebound hypertension. (2.4)

DOSAGE FORMS AND STRENGTHS

Extended-release oral suspension: 0.1 mg clonidine hydrochloride per mL (3)

CONTRAINDICATIONS

History of a hypersensitivity reaction to clonidine. Reactions have included generalized rash, urticaria, angioedema. (4)

WARNINGS AND PRECAUTIONS

- Hypotension/bradycardia: Titrate slowly and monitor vital signs frequently in patients at risk for hypotension, heart block, bradycardia, syncope, cardiovascular disease, vascular disease, cerebrovascular disease, or chronic renal failure. Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Avoid concomitant use of drugs with additive effects unless clinically indicated. Advise patients to avoid becoming dehydrated or overheated. (5.1)
- Somnolence/Sedation: Has been observed with clonidine. Consider the potential for additive sedative effects with CNS depressant drugs. Caution patients against operating heavy equipment or driving until they know how they respond to ONYDA XR (5.2)
- Cardiac Conduction Abnormalities: May worsen sinus node dysfunction and atrioventricular (AV) block, especially in patients taking other sympatholytic drugs. Titrate slowly and monitor vital signs frequently. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence at least 5% and twice the rate of placebo) as monotherapy in ADHD: somnolence, fatigue, irritability, nightmare, insomnia, constipation, dry mouth. (6.1)

Most common adverse reactions (incidence at least 5% and twice the rate of placebo) as adjunct therapy to psychostimulant in ADHD: somnolence, fatigue, decreased appetite, dizziness. (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.

DRUG INTERACTIONS

- CNS Depressants: Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs. (7)
- Tricyclic Antidepressants: May reduce the hypotensive effect of clonidine. (7)
- Drugs Known to Affect Sinus Node Function or AV Nodal Conduction: Avoid use of ONYDA XR with agents known to affect sinus node function or AV nodal conduction (e.g., digitalis, calcium channel blockers and beta-blockers) due to a potential for additive effects such as bradycardia and AV block. (7)
- Antihypertensive drugs: Use caution when coadministered with ONYDA XR. (7)

USE IN SPECIFIC POPULATIONS

Renal Impairment: The dosage of ONYDA XR must be adjusted according to the degree of impairment, and patients should be carefully monitored. (8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ONYDA XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy and as adjunctive therapy to central nervous system (CNS) stimulant medications in pediatric patients 6 years of age and older *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The starting dosage of ONYDA XR is 0.1 mg orally once daily at bedtime with or without food *[see Clinical Pharmacology (12.3)]*. Titrate the dose of ONYDA XR in increments of 0.1 mg per day at weekly intervals depending on clinical response up to the maximum recommended dosage of 0.4 mg once daily at bedtime.

Doses of ONYDA XR higher than 0.4 mg once daily were not evaluated in clinical trials for ADHD and are not recommended.

When ONYDA XR is added to a CNS stimulant, adjust the dose of the CNS stimulant depending on the clinical response to ONYDA XR.

2.2 Administration Instructions

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

- Use the oral dosing dispenser and bottle adapter provided with ONYDA XR.
- Ensure that the bottle adapter is firmly inserted into the bottle before first use and keep the adapter in place for the duration of the usage of the bottle.
- Gently shake ONYDA XR with a smooth up and down motion (to avoid foaming) for at least 10 seconds before each administration.
- For the bottles of 30 mL and 60 mL, discard any unused ONYDA XR 30 days after first opening the bottle.
- For the 120 mL bottle, discard any unused ONYDA XR 60 days after first opening the bottle.

2.3 Switching from Other Clonidine Products

For patients switching from another clonidine product, discontinue that treatment, and titrate with ONYDA XR using the titration schedule *[see Dosage and Administration (2.1)]*. Do not substitute for other clonidine products on a milligram-per-milligram basis because of differing pharmacokinetic profiles *[see Clinical Pharmacology (12.3)]*.

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2.4 Discontinuation

When discontinuing ONYDA XR, taper the total daily dose in decrements of no more than 0.1 mg every 3 to 7 days to avoid rebound hypertension *[see Warnings and Precautions (5.3)]*.

2.5 Missed Doses

If a dose of ONYDA XR is missed, skip that dose and take the next dose as scheduled. Do not take more than the prescribed total daily amount of ONYDA XR in any 24-hour period.

3 DOSAGE FORMS AND STRENGTHS

Extended-release oral suspension: Light beige to tan viscous suspension containing 0.1 mg clonidine hydrochloride per mL.

4 CONTRAINDICATIONS

ONYDA XR is contraindicated in patients with a history of a hypersensitivity reaction to clonidine. Reactions have included generalized rash, urticaria, and angioedema *[see Warnings and Precautions (5.4) and Adverse Reactions (6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension/Bradycardia

Treatment with ONYDA XR can cause dose-related decreases in blood pressure and heart rate *[see Adverse Reactions (6.1)]*. Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Titrate ONYDA XR slowly in patients with a history of hypotension, and those with underlying conditions that may be worsened by hypotension and bradycardia; e.g., heart block, bradycardia, cardiovascular disease, vascular disease, cerebrovascular disease, or chronic renal failure. In patients who have a history of syncope or may have a condition that predisposes them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration, advise patients to avoid becoming dehydrated or overheated. Monitor blood pressure and heart rate, and adjust dosages accordingly in patients treated concomitantly with antihypertensives or other drugs that can reduce blood pressure or heart rate or increase the risk of syncope *[see Drug Interactions (7)]*.

5.2 Sedation and Somnolence

Somnolence and sedation were commonly reported adverse reactions in clinical studies with clonidine hydrochloride extended-release tablets. In patients that completed 5 weeks of therapy in a controlled, fixed dose pediatric monotherapy study, 31% of patients treated with 0.4 mg/day and 38% treated with 0.2 mg/day versus 4% of placebo treated patients reported somnolence as an adverse reaction. In patients that completed 5 weeks of therapy in a controlled flexible dose pediatric adjunctive to stimulants study, 19% of patients treated with clonidine hydrochloride

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extended-release tablets plus a stimulant versus 7% treated with placebo plus a stimulant reported somnolence.

Before using ONYDA XR with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), consider the potential for additive sedative effects *[see Drug Interactions (7)]*. Caution patients against operating heavy equipment or driving until they know how they respond to treatment with ONYDA XR. Advise patients to avoid use with alcohol.

5.3 Rebound Hypertension

Abrupt discontinuation of ONYDA XR can cause rebound hypertension. In adults with hypertension, sudden cessation of clonidine extended-release formulation treatment in the 0.2 to 0.6 mg per day range resulted in reports of headache, tachycardia, nausea, flushing, warm feeling, brief lightheadedness, tightness in chest, and anxiety. In adults with hypertension, sudden cessation of treatment with immediate-release clonidine has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and tremor accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. Pediatric patients with gastrointestinal illnesses that lead to vomiting may result in missed doses of ONYDA XR, increasing the risk for rebound hypertension.

No studies evaluating abrupt discontinuation of clonidine hydrochloride extended-release tablets in pediatric patients with ADHD have been conducted; however, to minimize the risk of rebound hypertension, gradually reduce the dose of ONYDA XR in decrements of no more than 0.1 mg every 3 to 7 days. Patients should be instructed not to discontinue ONYDA XR therapy without consulting their physician due to the potential risk of withdrawal effects.

5.4 Allergic Reactions

In patients who have developed localized contact sensitization to clonidine transdermal system, continuation of clonidine transdermal system or use of oral ONYDA XR therapy may be associated with the development of a generalized skin rash.

In patients who develop an allergic reaction from clonidine transdermal system, use of ONYDA XR may also elicit an allergic reaction (including generalized rash, urticaria, or angioedema).

5.5 Cardiac Conduction Abnormalities

The sympatholytic action of clonidine may worsen sinus node dysfunction and atrioventricular (AV) block, especially in patients taking other sympatholytic drugs. There have been post-marketing reports of patients with conduction abnormalities and/or taking other sympatholytic drugs who developed severe bradycardia requiring intravenous (IV) atropine, IV isoproterenol, and temporary cardiac pacing while taking clonidine. Titrate ONYDA XR slowly and monitor vital signs frequently in patients with cardiac conduction abnormalities or patients concomitantly treated with other sympatholytic drugs.

6 ADVERSE REACTIONS

The following serious adverse reactions are described in greater detail elsewhere in labeling:

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- Hypotension/bradycardia *[see Warnings and Precautions (5.1)]*
- Sedation and somnolence *[see Warnings and Precautions (5.2)]*
- Rebound hypertension *[see Warnings and Precautions (5.3)]*
- Allergic reactions *[see Warnings and Precautions (5.4)]*
- Cardiac Conduction Abnormalities *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trial 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 practice.

The safety of ONYDA XR for the treatment of ADHD in pediatric patients 6 years and older is based upon adequate and well-controlled studies of clonidine hydrochloride extended-release tablets (referred to as "clonidine hydrochloride extended-release" in this section). The safety results of these adequate and well-controlled studies of clonidine hydrochloride extended-release tablets are presented below.

Two clonidine hydrochloride extended-release ADHD clinical studies (Study 1 and Study 2) evaluated 256 patients in two 8-week placebo-controlled studies.

A third clonidine hydrochloride extended-release ADHD clinical study (Study 3) evaluated 135 pediatric patients 6 to 17 years of age in a 40-week placebo-controlled randomized-withdrawal study.

Study 1: Fixed-dose clonidine hydrochloride extended-release Monotherapy

Study 1 was a short-term, multi-center, randomized, double-blind, placebo-controlled study of two fixed doses (0.2 mg/day or 0.4 mg/day) of clonidine hydrochloride extended-release in pediatric patients 6 to 17 years of age who met DSM-IV criteria for ADHD hyperactive or combined inattentive/hyperactive subtypes.

Most Common Adverse Reactions (incidence of ≥ 5% and at least twice the rate of placebo): somnolence, fatigue, irritability, insomnia, nightmare, constipation, dry mouth.

Adverse Reactions Leading to Discontinuation of clonidine hydrochloride extended-release: Five patients (7%) in the low dose group (0.2 mg), 15 patients (20%) in the high dose group (0.4 mg), and 1 patient in the placebo group (1%) reported adverse reactions that led to discontinuation. The most common adverse reactions that led to discontinuation were somnolence and fatigue.

Commonly observed adverse reactions (incidence of ≥2% in either active treatment group and greater than the rate on placebo) during the treatment period are listed in Table 1.

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Table 1: Common Adverse Reactions Occurring in ≥2%of Patients Treated with Clonidine Hydrochloride Extended-Release Tablets and Greater than the Rate of Placebo in the Fixed-Dose Monotherapy Trial -Treatment Period (Study 1)

Preferred Term	**Clonidine hydrochloride extended-release tablets 0.2 mg/day N=76** (%)	**Clonidine hydrochloride extended-release tablets 0.4 mg/day N=78** (%)	**Placebo N=76** (%)
PSYCHIATRIC DISORDERS			
Somnolence[*]	38	31	4
Nightmare	4	9	0
Emotional Disorder	4	4	1
Aggression	3	1	0
Tearfulness	1	3	0
Enuresis	0	4	0
Sleep Terror	3	0	0
Poor Quality Sleep	0	3	1
NERVOUS SYSTEM DISORDERS			
Headache	20	13	16
Insomnia	5	6	1
Tremor	1	4	0
Abnormal Sleep-Related Event	3	1	0
GASTRO-INTESTINAL DISORDERS			
Upper Abdominal Pain	15	10	12
Nausea	4	5	3
Constipation	1	6	0
Dry Mouth	0	5	1
GENERAL DISORDERS			
Fatigue[†]	16	13	1
Irritability	9	5	4
CARDIAC DISORDERS			
Dizziness	7	3	5
Bradycardia	0	4	0
INVESTIGATIONS			
Increased Heart Rate	0	3	0

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Preferred Term	Clonidine hydrochloride extended-release tablets 0.2 mg/day N=76 (%)	Clonidine hydrochloride extended-release tablets 0.4 mg/day N=78 (%)	Placebo N=76 (%)
METABOLISM AND NUTRITION DISORDERS			
Decreased Appetite	3	4	4

* Somnolence includes the terms "somnolence" and "sedation".
† Fatigue includes the terms "fatigue" and "lethargy".

Commonly observed adverse reactions (incidence of ≥2% in either active treatment group and greater than the rate on placebo) during the taper period are listed in Table 2.

Table 2: Common Adverse Reactions Occurring in ≥2% of Patients Treated with Clonidine Hydrochloride Extended-Release Tablets and Greater than the Rate of Placebo in the Fixed-Dose Monotherapy Trial -Taper Period* (Study 1)

Preferred Term	Clonidine hydrochloride extended-release tablets 0.2 mg/day N=76 (%)	Clonidine hydrochloride extended-release tablets 0.4 mg/day N=78 (%)	Placebo N=76 (%)
Abdominal Pain Upper	0	6	3
Headache	5	2	3
Gastrointestinal Viral	0	5	0
Somnolence	2	3	0
Heart Rate Increased	0	3	0
Otitis Media Acute	3	0	0

* Taper Period: 0.2 mg dose, week 8; 0.4 mg dose, weeks 6-8; Placebo dose, weeks 6-8

Study 2: Flexible-dose clonidine hydrochloride extended-release as Adjunctive Therapy to Psychostimulants

Study 2 was a short-term, randomized, double-blind, placebo-controlled study of a flexible dose of clonidine hydrochloride extended-release as adjunctive therapy to a psychostimulant in pediatric patients 6 to 17 years of age who met DSM-IV criteria for ADHD hyperactive or combined inattentive/hyperactive subtypes, during which clonidine hydrochloride extended-release was initiated at 0.1 mg/day and titrated up to 0.4 mg/day over a 3-week period.

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Most clonidine hydrochloride extended-release treated patients (75.5%) were escalated to the maximum dose of 0.4 mg/day.

Most Common Adverse Reactions (incidence of ≥ 5% and at least twice the rate of placebo): somnolence, fatigue, decreased appetite, dizziness.

Adverse Reactions Leading to Discontinuation: There was one patient in the clonidine hydrochloride extended-release + stimulant (group (1%) who discontinued because of an adverse event (severe bradyphrenia, with severe fatigue).

Commonly observed adverse reactions (incidence of ≥2% in the treatment group and greater than the rate on placebo) during the treatment period are listed in Table 3.

Table 3: Common Adverse Reactions Occurring in ≥2% of Patients Treated with Clonidine Hydrochloride Extended-Release Tablets and Greater than the Rate of Placebo in the Flexible-Dose Adjunctive to Stimulant Therapy Trial - Treatment Period (Study 2)

Preferred Term	**Clonidine hydrochloride extended-release tablets + Stimulant N=102** (%)	**PBO+Stimulant N=96** (%)
PSYCHIATRIC DISORDERS		
Somnolence+	19	7
Aggression	2	1
Affect Lability	2	1
Emotional Disorder	2	0
GENERAL DISORDERS		
Fatigue†	14	4
Irritability	2	7
NERVOUS SYSTEM DISORDERS		
Headache	7	12
Insomnia	4	3
GASTRO-INTESTINAL DISORDERS		
Upper Abdominal Pain	7	4
RESPIRATORY DISORDERS		
Nasal Congestion	2	2
METABOLISM AND NUTRITION DISORDERS		
Decreased Appetite	6	3

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Preferred Term	Clonidine hydrochloride extended-release tablets + Stimulant N=102 (%)	PBO+Stimulant N=96 (%)
CARDIAC DISORDERS		
Dizziness	5	1

[+]Somnolence includes the terms: "somnolence" and "sedation"
[†] Fatigue includes the terms "fatigue" and "lethargy"

Commonly observed adverse reactions (incidence of ≥2% in the treatment group and greater than the rate on placebo) during the taper period are listed in Table 4.

Table 4: Common Adverse Reactions Occurring in ≥2% of Patients Treated with Clonidine Hydrochloride Extended-Release Tablets and Greater than the Rate of Placebo in the Flexible-Dose Adjunctive to Stimulant Therapy Trial - Taper Period[+] (Study 2)

Preferred Term	Clonidine hydrochloride extended-release tablets + Stimulant N=102 (%)	Placebo+Stimulant N=96 (%)
Nasal Congestion	4	2
Headache	3	1
Irritability	3	2
Throat Pain	3	1
Gastroenteritis Viral	2	0
Rash	2	0

[+]Taper Period: weeks 6-8

Adverse Reactions Leading to Discontinuation

Thirteen percent (13%) of patients receiving clonidine hydrochloride extended-release discontinued from the pediatric monotherapy study due to adverse reactions, compared to 1% in the placebo group. The most common adverse reactions leading to discontinuation of clonidine hydrochloride extended-release monotherapy treated patients were somnolence/sedation (5%) and fatigue (4%).

Effect on Blood Pressure and Heart Rate

In patients that completed 5 weeks of treatment in a controlled, fixed-dose monotherapy study in pediatric patients, during the treatment period the maximum placebo-subtracted mean change in systolic blood pressure was -4.0 mmHg on clonidine hydrochloride extended-release 0.2 mg/day

and -8.8 mmHg on clonidine hydrochloride extended-release 0.4 mg/day. The maximum placebo-subtracted mean change in diastolic blood pressure was -4.0 mmHg on clonidine hydrochloride extended-release 0.2 mg/day and -7.3 mmHg on clonidine hydrochloride extended-release 0.4 mg/day. The maximum placebo-subtracted mean change in heart rate was -4.0 beats per minute on clonidine hydrochloride extended-release 0.2 mg/day and -7.7 beats per minute on clonidine hydrochloride extended-release 0.4 mg/day.

During the taper period of the fixed-dose monotherapy study the maximum placebo-subtracted mean change in systolic blood pressure was +3.4 mmHg on clonidine hydrochloride extended-release 0.2 mg/day and -5.6 mmHg on clonidine hydrochloride extended-release 0.4 mg/day. The maximum placebo-subtracted mean change in diastolic blood pressure was +3.3 mmHg on clonidine hydrochloride extended-release 0.2 mg/day and -5.4 mmHg on clonidine hydrochloride extended-release 0.4 mg/day. The maximum placebo-subtracted mean change in heart rate was -0.6 beats per minute on clonidine hydrochloride extended-release 0.2 mg/day and -3.0 beats per minute on clonidine hydrochloride extended-release 0.4 mg/day.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of clonidine hydrochloride extended-release tablets (and excludes those already mentioned in Section 6.1). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Psychiatric: hallucinations

Cardiovascular: Q-T prolongation

7 DRUG INTERACTIONS

The interactions of ONYDA XR with co-administration of other drugs have not been studied. The drug interaction data provided in this section is based on oral immediate-release clonidine formulations.

Table 5 displays clinically important drug interactions with ONYDA XR.

Table 5: Clinically Important Drug Interactions with ONYDA XR

Antihypertensive drugs	
Clinical Implication	Concomitant use of antihypertensive drugs with clonidine potentiates the hypotensive effects of clonidine.
Intervention	Monitor blood pressure and heart rate, and adjust dosage of ONYDA XR accordingly in patients treated concomitantly with antihypertensives *[see Warnings and Precautions (5.1)]*.

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CNS depressants	
Clinical Implication	Concomitant use of CNS depressants with clonidine potentiates the sedating effects *[see Warnings and Precautions (5.2)]*.
Intervention	Avoid concomitant use of CNS depressants with ONYDA XR.
Drugs that affect sinus node function or AV node conduction (e.g., digitalis, calcium channel blockers, beta blockers)	
Clinical Implication	Concomitant use of drugs that affect sinus node function or AV node conduction with clonidine potentiate bradycardia and risk of AV block *[see Warnings and Precautions (5.5)]*.
Intervention	Avoid concomitant use of drugs that affect sinus node function or AV node conduction with ONYDA XR.
Tricyclic antidepressants	
Clinical Implication	Concomitant use of tricyclic antidepressants with clonidine can increase blood pressure and may counteract the hypotensive effects of clonidine.
Intervention	Monitor blood pressure and adjust dosage of ONYDA XR as needed.

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, including ONYDA XR, during pregnancy. Healthcare providers are encouraged to advise patients to register by calling the National Pregnancy Registry for Psychiatric Medications at 1-866-961-2388 or visiting online at https://womensmentalhealth.org/adhd-medications/.

Risk Summary

Prolonged experience with clonidine in pregnant women over several decades, based on published literature, including controlled trials, a retrospective cohort study and case reports, have not identified a drug associated risk of major birth defects, miscarriage, and adverse maternal or fetal outcomes. In animal embryofetal studies, increased resorptions were seen in rats and mice administered oral clonidine hydrochloride from implantation through organogenesis at 10 and 5 times, respectively, the maximum recommended human dose

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(MRHD) given to adolescents on a mg/m^2 basis. No developmental effects were seen in rabbits administered oral clonidine hydrochloride during organogenesis at doses up to 3 times the MRHD *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Oral administration of clonidine hydrochloride to pregnant rabbits during the period of embryo/fetal organogenesis at doses of up to 80 mcg/kg/day (approximately 3 times the oral maximum recommended daily dose [MRHD] of 0.4 mg/day given to adolescents on a mg/m^2 basis) produced no developmental effects. In pregnant rats, however, doses as low as 15 mcg/kg/day (1/3 the MRHD given to adolescents on a mg/m^2 basis) were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating and throughout gestation. Increased resorptions were not associated with treatment at the same or at higher dose levels (up to 3 times the MRHD) when treatment of the dams was restricted to gestation days 6-15. Increases in resorptions were observed in both rats and mice at 500 mcg/kg/day (10 and 5 times the MRHD in rats and mice, respectively) or higher when the animals were treated on gestation days 1-14; 500 mcg/kg/day was the lowest dose employed in this study.

8.2 Lactation

Risk Summary

Based on published lactation studies, clonidine hydrochloride is present in human milk at relative infant doses ranging from 4.1% to 8.4% of the maternal weight-adjusted dosage. Although in most cases, there were no reported adverse effects in breastfed infants exposed to clonidine, there is one case report of sedation, hypotonia, and apnea in an infant exposed to clonidine through breast milk. If an infant is exposed to clonidine through breastmilk, monitor for symptoms of hypotension and bradycardia, such as sedation, lethargy, tachypnea and poor feeding *(see Clinical Considerations)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ONYDA XR and any potential adverse effects on the breastfed child from ONYDA XR or from the underlying maternal condition. Exercise caution when ONYDA XR is administered to a nursing woman.

Clinical Considerations

Monitor breastfeeding infants exposed to ONYDA XR through breast milk for symptoms of hypotension and/or bradycardia such as sedation, lethargy, tachypnea, and poor feeding.

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8.3 Females and Males of Reproductive Potential

Infertility

Findings in animal studies revealed that ONYDA XR may impair fertility in females and males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and efficacy of clonidine hydrochloride extended-release in the treatment of ADHD have been established in pediatric patients 6 to 17 years of age. Use of clonidine hydrochloride extended-release in pediatric patients 6 to 17 years of age is supported by three adequate and well-controlled studies; a short-term, placebo-controlled monotherapy trial, a short-term adjunctive therapy trial and a longer-term randomized monotherapy trial *[see Clinical Studies (14)]*. Safety and efficacy in pediatric patients below the age of 6 years has not been established.

Juvenile Animal Data

In studies in juvenile rats, clonidine hydrochloride alone or in combination with methylphenidate had an effect on bone growth at clinically relevant doses and produced a slight delay in sexual maturation in males at 3 times the maximum recommended human dose (MRHD) for clonidine and methylphenidate.

In a study where juvenile rats were treated orally with clonidine hydrochloride from day 21 of age to adulthood, a slight delay in onset of preputial separation (delayed sexual maturation) was seen in males treated with 300 mcg/kg/day, which is approximately 3 times the MRHD of 0.4 mg/day on a mg/m^2 basis. The no-effect dose was 100 mcg/kg/day, which is approximately equal to the MRHD. There was no drug effects on fertility or on other measures of sexual or neurobehavioral development.

In a study where juvenile rats were treated with clonidine alone (300 mcg/kg/day) or in combination with methylphenidate (10 mg/kg/day in females and 50/30 mg/kg/day in males; the dose was lowered from 50 to 30 mg/kg/day in males due to self-injurious behavior during the first week of treatment) from day 21 of age to adulthood, decreases in bone mineral density and mineral content were observed in males treated with 300 mcg/kg/day clonidine alone and in combination with 50/30 mg/kg/day methylphenidate and a decrease in femur length was observed in males treated with the combination at the end of the treatment period. These doses are approximately 3 times the MRHD of 0.4 mg/day clonidine and 54 mg/day methylphenidate on a mg/m^2 basis. All these effects in male were not reversed at the end of a 4-week recovery period. In addition, similar findings were seen in males treated with a lower dose of clonidine (30 mcg/kg/day) in combination with 50 mg/kg/day of methylphenidate and a decrease in femur length was observed in females treated with clonidine alone at the end of the recovery period. These effects were accompanied by a decrease in body weight gain in treated animals during the treatment period but the effect was reversed at the end of the recovery period. A delay in preputial separation (sexual maturation) was observed in males treated with the combination treatment of 300 mcg/kg/day clonidine and 50/30 mg/kg/day methylphenidate. There was no effect on reproduction or sperm analysis in these males.

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8.6 Renal Impairment

The impact of renal impairment on the pharmacokinetics of clonidine in pediatric patients has not been assessed. The initial dosage of ONYDA XR should be based on degree of impairment. Monitor patients carefully for hypotension and bradycardia, and titrate to higher doses cautiously. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental ONYDA XR following dialysis.

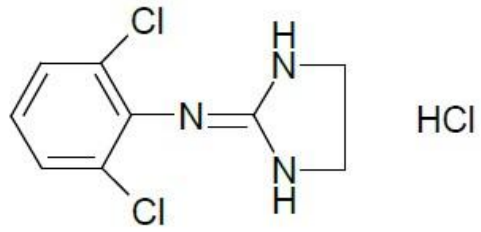
10 OVERDOSAGE

Hypertension may develop early and may be followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability and miosis. The frequency of CNS depression may be higher in pediatric patients than adults. Large overdoses may result in reversible cardiac conduction defects or dysrhythmias, apnea, coma and seizures. Signs and symptoms of overdose generally occur within 30 minutes to two hours after exposure.

Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

ONYDA XR contains clonidine hydrochloride, a centrally acting alpha$_2$-adrenergic agonist. Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical name is 2-[(2,6-dichlorophenyl)imino]imidazolidine hydrochloride. The following is the structural formula:



The molecular formula of clonidine hydrochloride is $C_9H_9Cl_2N_3$•HCl and the molecular weight is 266.5. The pKa is 8.05.

Clonidine hydrochloride is an odorless, bitter, white to almost white, crystalline powder soluble in water and alcohol. The pH of a 5% solution in water is between 3.5 and 5.5.

ONYDA XR is an extended-release suspension for oral administration. Each mL of ONYDA XR contains 0.09 mg clonidine equivalent to 0.1 mg clonidine hydrochloride (0.095 mg clonidine hydrochloride complexed with sodium polystyrene sulfonate and 0.005 mg clonidine hydrochloride). The pH of ONYDA XR is between 2.8 and 4.

The inactive ingredients are anhydrous citric acid, edetate disodium, glycerin, modified starch, methylparaben, orange flavor, polyvinyl acetate dispersion 30%, povidone, polysorbate 80, propylparaben, purified water, sucrose, sodium polystyrene sulfonate, triacetin, xanthan gum.

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Clonidine stimulates alpha$_2$-adrenergic receptors in the brain. Clonidine is not a central nervous system stimulant. The mechanism of action of clonidine in ADHD is not known.

12.2 Pharmacodynamics

Clonidine is a known antihypertensive agent. By stimulating alpha$_2$-adrenergic receptors in the brain stem, clonidine reduces sympathetic outflow from the central nervous system and decreases peripheral resistance, renal vascular resistance, heart rate, and blood pressure.

12.3 Pharmacokinetics

Immediate-release clonidine hydrochloride, extended-release clonidine hydrochloride tablets, and ONYDA XR have different pharmacokinetic characteristics. Dose substitution on a milligram for milligram basis will result in differences in exposures *[see Dosage and Administration (2.3)]*.

Absorption

Following a single 0.2 mg dose of ONYDA XR in 20 healthy adult subjects under fasting conditions in a crossover study, the median (range) time to peak plasma concentrations (T_{max}) for clonidine was 7.50 (4 –17) hours after dosing. Peak concentration (C_{max}) was 95.6% of the C_{max} of clonidine extended-release tablet 0.1 mg administered at 0 and 12 hours under fasting conditions. The relative bioavailability of ONYDA XR compared with an equal dose of clonidine extended-release tablet was 96.1%.

After oral administration of 0.2 mg of ONYDA XR once daily over 5 days under fasted conditions in healthy adult subjects, the peak steady state plasma concentration (C_{max}.ss) was 107.9%, and steady state relative bioavailability (AUC_t, ss) was 97.7% compared with 0.1 mg of clonidine extended-release tablet administered twice daily under fasting conditions. The minimum concentration at steady state (Cmin,ss) of ONYDA XR was about 26% lower than that of the equal dose of clonidine extended-release tablet.

Following oral administration of an immediate release formulation in healthy adult subjects, plasma clonidine concentration peaks in approximately 3 to 5 hours.

A comparison across studies suggests that the C_{max} is 50% lower for clonidine hydrochloride extended-release tablets compared to immediate-release clonidine hydrochloride.

Effect of Food

Food had no effect on plasma exposures of clonidine after administration of ONYDA XR (see Figure 1).

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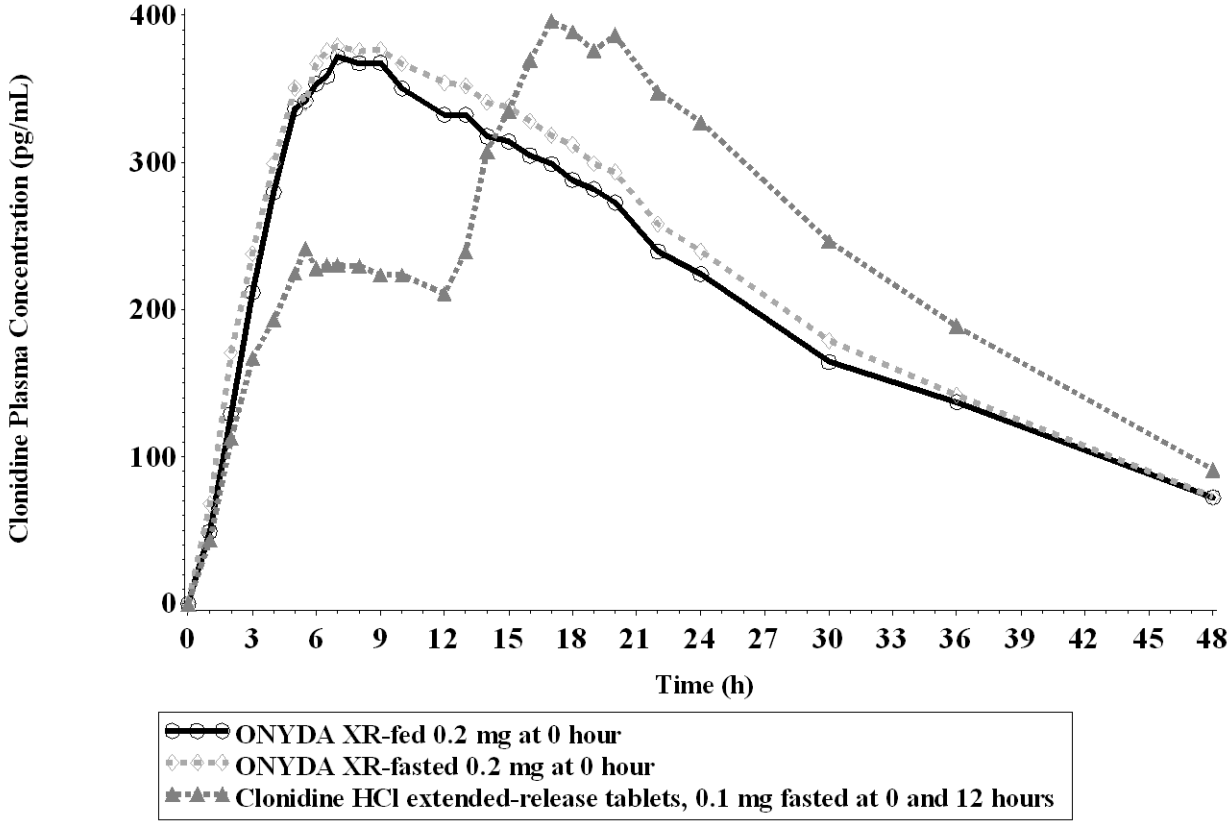
Figure 1: Mean Clonidine Concentration-Time Profiles After Single Dose Administration



Elimination

The plasma half-life of immediate-release clonidine ranges from 12 to 16 hours. The half-life increases up to 41 hours in patients with severe impairment of renal function.

Metabolism

About 50% of the absorbed dose is metabolized in the liver.

Excretion

Following oral administration about 40% to 60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. Although studies of the effect of renal impairment and studies of clonidine excretion have not been performed with ONYDA XR, results are expected to be similar to those of the immediate-release formulation.

Specific Populations

Pediatric patients

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Plasma clonidine concentrations in pediatric patients 6 to 17 years (0.1 mg twice daily and 0.2 mg twice daily of clonidine hydrochloride extended-release tablets) with ADHD are greater than those of adults with hypertension, with pediatric patients 6 to 17 years receiving higher doses on a mg/kg basis. Body weight normalized clearance (CL/F) in pediatric patients aged 6 to 17 years was higher than CL/F observed in adults with hypertension. Clonidine concentrations in plasma increased with increases in dose over the dose range of 0.2 to 0.4 mg/day. Clonidine CL/F was independent of dose administered over the 0.2 to 0.4 mg/day dose range. Clonidine CL/F appeared to decrease slightly with increases in age over the range of 6 to 17 years, and females had a 23% lower CL/F than males. The incidence of "sedation-like" events (somnolence and fatigue) appeared to be independent of clonidine dose or concentration within the studied dose range in the titration study. Results from the add-on study showed that clonidine CL/F was 11% higher in patients who were receiving methylphenidate and 44% lower in those receiving amphetamine compared to subjects not on adjunctive therapy.

Drug Interaction Studies

Alcohol: In an *in vitro* alcohol-induced dose dumping study, a significantly faster and more variable ONYDA XR drug release was observed in the presence of 20% alcohol, but not with 5% or 10% alcohol, when compared to 0% alcohol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Carcinogenesis

Clonidine hydrochloride was not carcinogenic when administered in the diet of rats (for up to 132 weeks) or mice (for up to 78 weeks) at doses of up to 1,620 (male rats), 2,040 (female rats), or 2,500 (mice) mcg/kg/day. These doses are approximately 20, 25, and 15 times, respectively, the maximum recommended human dose (MRHD) of 0.4 mg/day on a mg/m^2 basis.

Mutagenesis

There was no evidence of genotoxicity in the Ames test for mutagenicity or mouse micronucleus test for clastogenicity.

Impairment of Fertility

In a reproduction study fertility of female rats appeared to be adversely affected at dose levels of 500 and 2,000 mcg/kg/day (10 and 40 times the MRHD on a mg/m^2 basis). Lower doses have not been adequately evaluated and a no adverse effect level could not be established.

14 CLINICAL STUDIES

The efficacy of ONYDA XR for the treatment of ADHD in pediatric patients 6 years of age and older is based upon adequate and well-controlled studies of clonidine hydrochloride extended-release tablets (referred to as “clonidine hydrochloride extended-release” in this section). The

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efficacy results of these adequate and well-controlled studies of clonidine hydrochloride extended-release tablets are presented below.

Efficacy of clonidine hydrochloride extended-release in the treatment of ADHD was established in pediatric patients 6 to 17 years in:

- One short-term, placebo-controlled monotherapy trial (Study 1)
- One short-term adjunctive therapy to psychostimulants trial (Study 2)
- One randomized withdrawal trial as monotherapy (Study 3)

Short-term Monotherapy and Adjunctive Therapy to Psychostimulant Studies for ADHD

The efficacy of clonidine hydrochloride extended-release in the treatment of ADHD was established in 2 (one monotherapy and one adjunctive therapy) placebo-controlled trials in pediatric patients aged 6 to 17 years, who met DSM-IV criteria of ADHD hyperactive or combined hyperactive/inattentive subtypes. Signs and symptoms of ADHD were evaluated using the investigator administered and scored ADHD Rating Scale-IV-Parent Version (ADHDRS-IV) total score including hyperactive/impulsivity and inattentive subscales. Study 1 was an 8-week randomized, double-blind, placebo-controlled, fixed dose study of pediatric patients 6 to 17 years (N=236) with a 5-week primary efficacy endpoint. Patients were randomly assigned to one of the following three treatment groups: clonidine hydrochloride extended-release 0.2 mg/day (N=78), clonidine hydrochloride extended-release 0.4 mg/day (N=80), or placebo (N=78). Dosing for the clonidine hydrochloride extended-release groups started at 0.1 mg/day and was titrated in increments of 0.1 mg/week to their respective dose (as divided doses). Patients were maintained at their dose for a minimum of 2 weeks before being gradually tapered down to 0.1 mg/day at the last week of treatment. At both doses, improvements in ADHD symptoms were statistically significantly superior in clonidine hydrochloride extended-release-treated patients compared with placebo-treated patients at the end of 5 weeks as measured by the ADHDRS-IV total score (Table 6). Study 2 was an 8-week randomized, double-blind, placebo-controlled, flexible dose study in pediatric patients 6 to 17 years (N=198) with a 5-week primary efficacy end point. Patients had been treated with a psychostimulant (methylphenidate or amphetamine) for four weeks with inadequate response. Patients were randomly assigned to one of two treatment groups: clonidine hydrochloride extended-release adjunct to a psychostimulant (N=102) or psychostimulant alone (N=96). The clonidine hydrochloride extended-release dose was initiated at 0.1 mg/day and doses were titrated in increments of 0.1 mg/week up to 0.4 mg/day, as divided doses, over a 3-week period based on tolerability and clinical response. The dose was maintained for a minimum of 2 weeks before being gradually tapered to 0.1 mg/day at the last week of treatment. ADHD symptoms were statistically significantly improved in clonidine hydrochloride extended-release plus stimulant group compared with the stimulant alone group at the end of 5 weeks as measured by the ADHDRS-IV total score (Table 6).

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Table 6: Short-Term Trials

Study Number	Treatment Group	Primary Efficacy Measure: ADHDRS-IV Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	Clonidine hydrochloride extended-release tablets (0.2 mg/day)	43.8 (7.47)	-15.0 (1.38)	-8.5 (-12.2, -4.8)
	Clonidine hydrochloride extended-release tablets (0.4 mg/day)	44.6 (7.73)	-15.6 (1.33)	-9.1 (-12.8, -5.5)
	Placebo	45.0 (8.53)	-6.5 (1.35)	----------
Study 2	Clonidine hydrochloride extended-release tablets (0.4 mg/day) + Psychostimulant	38.9 (6.95)	-15.8 (1.18)	-4.5 (-7.8, -1.1)
	Psychostimulant alone	39.0 (7.68)	-11.3 (1.24)	----------

[a] Difference (drug minus placebo) in least-squares mean change from baseline. SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

Maintenance Monotherapy for ADHD

Study 3 was a double-blind, placebo-controlled, randomized-withdrawal study in pediatric patients 6 to 17 years (n=253) with DSM-IV-TR diagnosis of ADHD. The study consisted of a 10-week, open-label phase (4 weeks of dose optimization and 6 weeks of dose maintenance), a 26-week double-blind phase, and a 4-week taper-down and follow-up phase. All patients were initiated at 0.1 mg/day and increased at weekly intervals in increments of 0.1 mg/day until reaching personalized optimal dose (0.1, 0.2, 0.3 or 0.4 mg/day, as divided doses). Eligible patients had to demonstrate treatment response as defined by ≥ 30% reduction in ADHD-RS-IV total score and a Clinical Global Impression-Improvement score of 1 or 2 during the open label phase. Patients who sustained treatment response (n=135) until the end of the open label phase were randomly assigned to one of the two treatment groups, clonidine hydrochloride extended-release (N=68) and Placebo (N=67), to evaluate the long-term efficacy of maintenance dose of clonidine hydrochloride extended-release in the double-blind phase. The primary efficacy endpoint was the percentage of patients with treatment failure defined as a ≥ 30% increase (worsening) in ADHD-RS-IV total score and ≥ 2 points increase (worsening) in Clinical Global Impression – Severity Scale in 2 consecutive visits or early termination for any reason. A total of 73 patients experienced treatment failure in the double-blind phase: 31 patients (45.6%) in the clonidine hydrochloride extended-release group and 42 patients (62.7%) in the placebo group, with a statistically significant difference in the primary endpoint favoring clonidine (Table 7).

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The cumulative proportion of patients with treatment failure over time during the double-blind phase is displayed in Figure 2.

Table 7: Treatment Failure: Double-Blind Full Analysis Set (Study 3)

Study 3	**Double-Blind Full Analysis Set**	
	Clonidine Hydrochloride Extended-Release Tablets	**Placebo**
Number of patients	68	67
Number of treatment failures	31 (45.6%)	42 (62.7%)
Basis of Treatment Failure		
Clinical criteria[a,b]	11 (16.2%)	9 (13.4%)
Lack of efficacy[c]	1 (1.5%)	3 (4.5%)
Withdrawal of informed assent/consent	4 (5.9%)	20 (29.9%)
Other early terminations	15 (22.1%)	10 (14.9%)

ADHD-RS-IV = Attention Deficit Hyperactivity Disorder-Rating Scale-4th edition; CGI-S = Clinical Global Impression-Severity

[a] [a] At the same 2 consecutive visits a (1) 30% or greater reduction in ADHD-RS-IV, and (2) 2-point or more increase in CGI-S.

[b] [b]Two patients (1 placebo and 1 clonidine hydrochloride extended-release tablets) withdrew consent, but met the clinical criteria for treatment failure.

[c] [c]Three patients (all placebo) discontinued the study due to treatment failure, but met only the criterion for ADHD-RS-IV.

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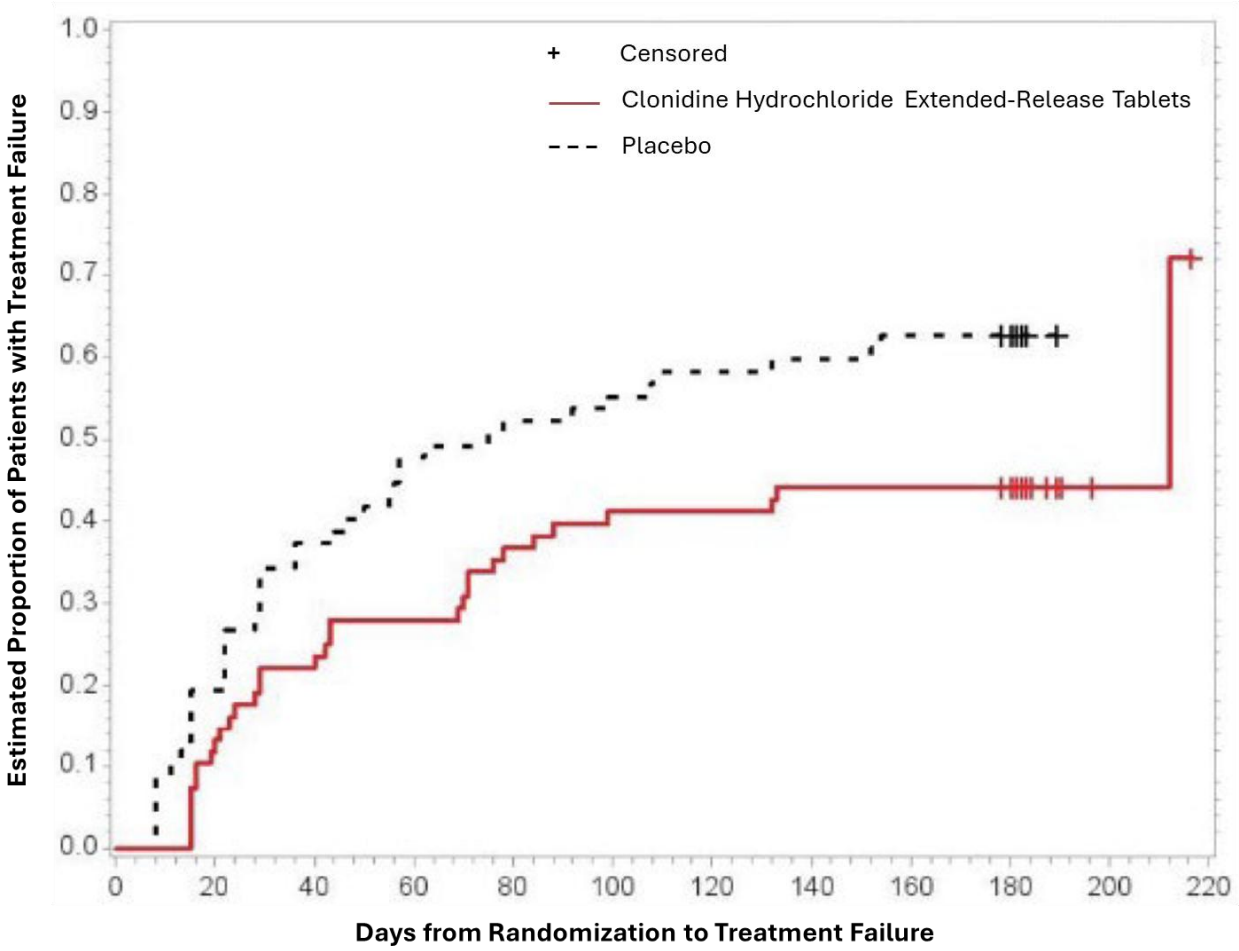
Figure 2: Kaplan-Meier Estimation of Cumulative Proportion of Pediatric Patients (6 to 17 Years) with Treatment Failure (Study 3)



16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ONYDA XR (clonidine hydrochloride) extended-release oral suspension 0.1 mg/mL is a light beige to tan viscous suspension.

ONYDA XR is supplied in a carton. Each carton contains one bottle with a child resistant closure, an oral dosing dispenser(s), and a press in bottle adapter(s).

Bottle of 30 mL	NDC 24478-148-03	One (1) oral dosing dispenser and one (1) press in bottle adapter

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Bottle of 60 mL	NDC 24478-148-04	One (1) oral dosing dispenser and one (1) press in bottle adapter
Bottle of 120 mL	NDC 24478-148-02	Two (2) oral dosing dispensers and two (2) press in bottle adapters

Storage and Handling

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

Store and dispense ONYDA XR in the original bottle. Dispense with bottle adapter and oral dosing dispenser supplied in the carton.

For the bottles of 30 mL and 60 mL, discard any unused ONYDA XR 30 days after first opening the bottle.

For the 120 mL bottle, discard any unused ONYDA XR 60 days after first opening the bottle.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Dosage and Administration

Advise patients that ONYDA XR may be taken with or without food. When initiating treatment, provide titration instructions *[see Dosage and Administration (2.1)]*.

Administration Instructions

Instruct patients to read the "Instructions for Use" for complete administration instructions *[see Dosage and Administration (2.2)]*.

Advise patients to:

- firmly insert the bottle adapter into the bottle and do not remove the bottle adapter once inserted. Use the oral dispenser provided with ONYDA XR.
- gently shake ONYDA XR with a smooth up and down motion (to avoid foaming) for at least 10 seconds before each administration.
- For the bottles of 30 mL and 60 mL, discard any unused ONYDA XR 30 days after first opening the bottle.
- For the 120 mL bottle, discard any unused ONYDA XR 60 days after first opening the bottle.

Missed Dose

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If patients miss a dose of ONYDA XR, advise them to skip the dose and take the next dose as scheduled and not to take more than the prescribed total daily amount of ONYDA XR in any 24-hour period *[see Dosage and Administration (2.5)]*.

Hypotension/Bradycardia

Advise patients who have a history of syncope or may have a condition that predisposes them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration, to avoid becoming dehydrated or overheated *[see Warnings and Precautions (5.1)]*.

Sedation and Somnolence

Instruct patients to use caution when driving a car or operating heavy equipment until they know how they will respond to treatment with ONYDA XR. Also advise patients to avoid the use of ONYDA XR with other centrally active depressants and with alcohol *[see Warnings and Precautions (5.2)]*.

Rebound Hypertension

Advise patients not to discontinue ONYDA XR abruptly. Inform patients and caregivers that pediatric patients with gastrointestinal illnesses that lead to vomiting may be at increased risk for rebound hypertension *[see Warnings and Precautions (5.3)]*.

Allergic Reactions

Advise patients to discontinue ONYDA XR and seek immediate medical attention if any signs or symptoms of a hypersensitivity reaction occur, such as generalized rash, urticaria, or angioedema *[see Warnings and Precautions (5.4)]*.

Pregnancy Registry

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

Lactation

Advise breastfeeding women using ONYDA XR to monitor infants for excess sedation, decreased muscle tone, and respiratory depression and to seek medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

Fertility

Advise females and males of reproductive potential that ONYDA XR may impair fertility *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)]*

Manufactured by/Distributed by:

Tris Pharma, Inc.

Monmouth Junction, NJ 08852

www.trispharma.com

LB8735

Rev. 05

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PATIENT INFORMATION
ONYDA™ XR (oh-nee-dah)
(clonidine hydrochloride)
extended-release oral suspension

What is ONYDA XR?

ONYDA XR is a prescription medicine used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) alone or with certain other ADHD medicines in children 6 years of age and older.

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

Who should not take ONYDA XR?

Do not take ONYDA XR if you are allergic to clonidine. See the end of this Patient Information for a complete list of ingredients in ONYDA XR.

Before taking ONYDA XR, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems
- have low or high blood pressure
- have a history of passing out (syncope)
- have heart problems, including slow heart rate or other heart rhythm problems
- had a stroke or have stroke symptoms
- had an allergic reaction after taking clonidine through your skin in a transdermal system (patch)
- are pregnant or plan to become pregnant. It is not known if ONYDA XR will harm the unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
  - There is a pregnancy registry for females who are exposed to ADHD medications, including ONYDA XR, during pregnancy. The purpose of the registry is to collect information about the health of females exposed to ONYDA XR and their baby. If you become pregnant during treatment with ONYDA XR, talk to your healthcare provider about registering with the National Pregnancy Registry of ADHD Medications at 1-866-961-2388 or visit online at https://womensmentalhealth.org/adhdmedications/
- are breastfeeding or plan to breastfeed. ONYDA XR passes into the breast milk. Babies who are breastfed during treatment with ONYDA XR may become very sleepy, develop relaxed or floppy muscles, and develop trouble breathing. Call the baby's healthcare provider if the baby is breastfed during treatment with ONYDA XR and develops any of these symptoms. Talk to your healthcare provider about the best way to feed your baby if you take ONYDA XR.

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

ONYDA XR and certain other medicines may affect each other causing serious side effects. **Especially tell your healthcare provider if you take:**

- anti-depression medicines
- heart or blood pressure medicines
- other medicines for ADHD
- other medicines that contain clonidine
- medicines that cause sleepiness (sedation)

Ask your healthcare provider or pharmacist if you are not sure if your medicine is listed above.

Know the medicines that you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take ONYDA XR?

- Take ONYDA XR 1 time daily at bedtime with or without food.
- Take ONYDA XR exactly as your healthcare provider tells you.
- Your healthcare provider may change your dose of ONYDA XR. Do not change your dose of ONYDA XR without talking to your healthcare provider.
- **If you are taking another clonidine medicine**, **stop taking it** before you start treatment with ONYDA XR.
- **The dose of ONYDA XR is not the same as other clonidine medicines. Do not** change between ONYDA XR and other clonidine medicines unless your healthcare provider tells you.
- **Do not** stop taking ONYDA XR without talking to your healthcare provider.
- If you miss a dose of ONYDA XR, skip the missed dose and take the next dose at their regular scheduled time. Do not take more ONYDA XR in a 24-hour period than your healthcare provider prescribed for your daily dose.
- For the bottles of 30 mL and 60 mL, throw away (discard of) any remaining ONYDA XR if you have not used it 30 days after first opening the bottle.
- For the 120 mL bottle, throw away (discard of) any remaining ONYDA XR if you have not used it 60 days after first opening the bottle.

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See the detailed Instructions for Use for information on how to take a dose of ONYDA XR.

If you take too much ONYDA 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 ONYDA XR?

- **Do not** become dehydrated or too hot (overheated) to decrease your chance of passing out during treatment with ONYDA XR.
- **Do not** drive, operate heavy machinery, or do other dangerous activities until you know how ONYDA XR affects you because ONYDA XR can cause sleepiness and tiredness that could cause slow reaction times.
- **Do not** drink alcohol or take other medicines that make you sleepy or dizzy during treatment with ONYDA XR until you talk with your healthcare provider. Taking ONYDA XR with alcohol or medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse.
- Do not suddenly stop ONYDA XR. Tell your healthcare provider if you have been vomiting and cannot take ONYDA XR, you may be at risk for rebound hypertension.

What are possible side effects of ONYDA XR?

ONYDA XR may cause serious side effects, including:

- **Decreased blood pressure and heart rate.** ONYDA XR can decrease your blood pressure and heart rate, which can increase your chance of passing out (syncope). If you have a history of passing out or have other medical problems or take other medicines that increase your risk of passing out, your risk is higher. Your healthcare provider should check your heart rate and blood pressure before starting treatment and regularly during treatment with ONYDA XR. See "**What should I avoid while taking ONYDA XR?**"
- **Sleepiness and tiredness that could cause slow reaction times (sedation and somnolence).** See "**What should I avoid while taking ONYDA XR?**"
- **Rebound high blood pressure (hypertension).** Suddenly stopping ONYDA XR can cause high blood pressure to return if you have a history of high blood pressure. **Suddenly stopping ONYDA XR may also cause withdrawal symptoms** including headache, increased heart rate, nausea, flushing or warm feeling, lightheadedness, tightness in your chest and nervousness or anxiety. **Do not suddenly stop ONYDA XR treatment without first talking to your healthcare provider.**
- **Allergic reactions.** You may develop an allergic reaction to ONYDA XR if you had an allergic reaction to clonidine taken through your skin in a patch. Stop taking ONYDA XR and call your healthcare provider right away or go to the nearest emergency room if you develop any signs or symptoms of an allergic reaction, including:
  - skin rash
  - hives
  - swelling of the eyes, face, lips, or tongue

The most common side effects of ONYDA XR when used alone include:

- falling asleep or sleepiness and tiredness that could cause slow reaction times
- irritability
- nightmare
- trouble sleeping
- constipation
- dry mouth

The most common side effects of ONYDA XR when used with other ADHD medicines include:

- falling asleep or sleepiness and tiredness that could cause slow reaction times
- decreased appetite
- dizziness

ONYDA XR may cause fertility problems in females and males, which may affect your ability to have a child. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of ONYDA 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 ONYDA XR?

- Store ONYDA XR at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect from light and keep ONYDA XR in the original container. Tightly close the child-resistant cap.
- For the bottles of 30 mL and 60 mL, throw away (discard of) any remaining ONYDA XR if you have not used it 30 days after first opening the bottle.
- For the 120 mL bottle, throw away (discard of) any remaining ONYDA XR if you have not used it 60 days after first opening the bottle.
- **Keep ONYDA XR and all medicines out of the reach of children.**

General information about the safe and effective use of ONYDA XR.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ONYDA XR for a condition for which it was not prescribed. Do not give ONYDA XR to other people, even if they have the same symptoms that you have. It may harm them. You can also ask your pharmacist or healthcare provider for information about ONYDA XR that is written for health professionals.

What are the ingredients in ONYDA XR?

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Active Ingredient: clonidine hydrochloride
Inactive Ingredients: anhydrous citric acid, edetate disodium, glycerin, modified starch, methylparaben, orange flavor, polyvinyl acetate dispersion 30%, povidone, polysorbate 80, propylparaben, purified water, sucrose, sodium polystyrene sulfonate, triacetin, and xanthan gum

Manufactured by/Distributed by:
Tris Pharma, Inc.
Monmouth Junction, NJ 08852
www.trispharma.com
For more information about ONYDA XR call 1-732-940-0358.
Rev. 04

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 04/2025

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INSTRUCTIONS FOR USE
ONYDA^{TM} XR (oh-nee-dah)
(clonidine hydrochloride)
extended-release oral suspension

This Instructions for Use contains information on how to take ONYDA XR.

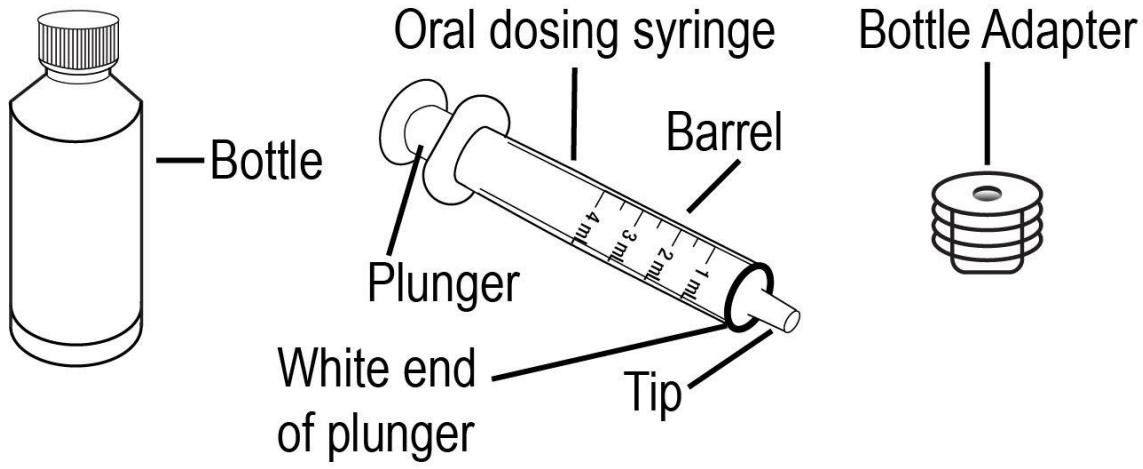
Important Information You Need to Know Before Taking ONYDA XR:

- ONYDA XR is for oral use only (taken by mouth).
- Take ONYDA XR with or without food.
- Use only the oral dosing syringe and bottle adapter that come with ONYDA XR to measure and take a dose of ONYDA XR.
- Shake the ONYDA XR bottle gently.
- Check the expiration date (EXP) on the carton label. Do not take ONYDA XR after the expiration date has passed. Call your healthcare provider or pharmacist if your medicine is expired.
- For the bottles of 30 mL and 60 mL, throw away (discard of) any remaining ONYDA XR if you have not used it 30 days after first opening the bottle.
- For the 120 mL bottle, throw away (discard of) any remaining ONYDA XR if you have not used it 60 days after first opening the bottle.

Supplies included in the ONYDA XR carton:

1 bottle of ONYDA XR	**Dosing Syringe(s)**	**Bottle Adapter(s)**
30 mL bottle	1	1
60 mL bottle	1	1
120 mL bottle	2	2

Figure A



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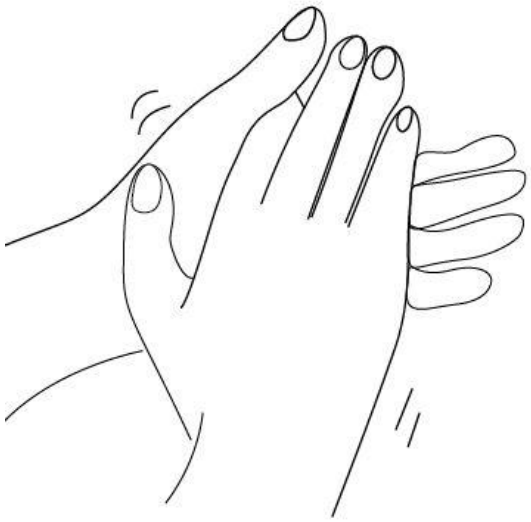
Step 1:

Preparing to take ONYDA XR:

- Wash and dry your hands (see Figure B).
- Remove the ONYDA XR bottle, 1 oral dosing syringe, and 1 bottle adapter from the carton.

Tell your pharmacist right away if you are missing any supplies from the carton.

Figure B



Step 2:

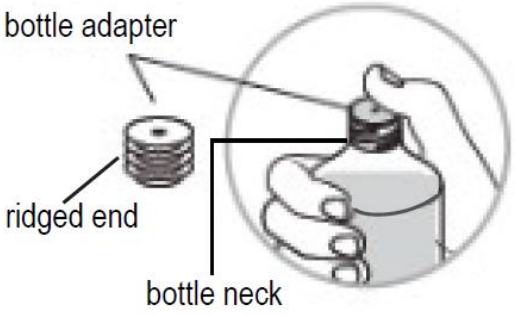
- Place the ONYDA XR bottle on a flat surface like a table or countertop and remove the child resistant cap by pressing down and turning counterclockwise (see Figure C).

Figure C

Insert the bottle adapter (first time use only).

- Hold the bottle firmly and insert the ridged end of the bottle adapter into the neck of the bottle.
- Firmly push the bottle adapter all the way down with your thumb until the top of the adapter is aligned and flat (flush) with the top of the bottle (See Figure D).
- Do not remove the bottle adapter once it has been inserted into the bottle.

Figure D



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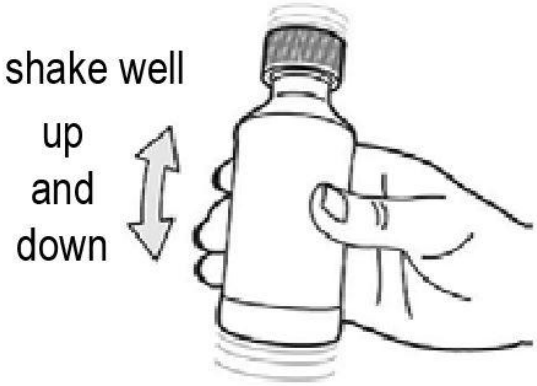
Step 3:

- Put the cap back on the bottle and close it tightly by turning the cap clockwise (see Figure E).

Figure E

- Shake the bottle gently with a smooth up and down motion to avoid foaming (see Figure F).
- Shake the bottle gently for at least 10 seconds before you take each dose.

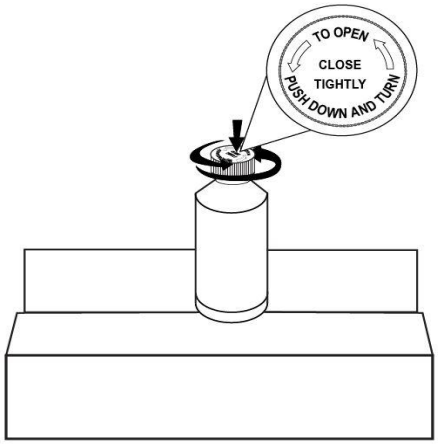
Figure F



Step 4:

- Place the ONYDA XR bottle upright on the table or countertop. Open the cap again by pressing down and turn counterclockwise to remove the cap (see Figure G).

Figure G



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Step 5:

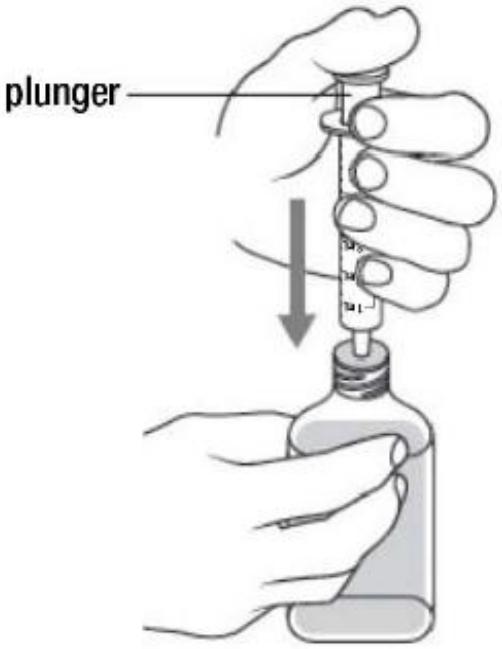
- Check the ONYDA XR oral dosing syringe to find the right dose in milliliters (mL) that has been prescribed by the healthcare provider (see Figure H).
- Make sure the oral dosing syringe is dry.

Figure H

Step 6:

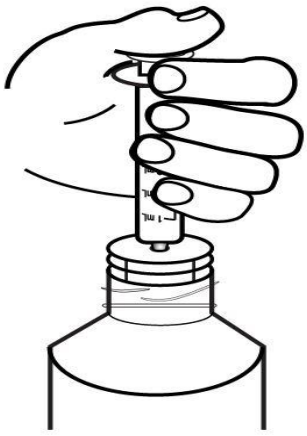
- Insert the tip of the oral dosing syringe through the adapter into the bottle (see Figure I).

Figure I



- Push the plunger all the way down (see Figure J).

Figure J



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Step 7:

Measuring the dose of ONYDA XR:

- With the tip of the oral dosing syringe in place in the adapter, hold the ONYDA 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 mL you need for the prescribed dose (see Figure K).
- Push and pull the plunger a few times to make sure that there are no air bubbles.
- Tap the barrel of the oral dosing syringe if needed to get rid of any air bubbles (see Figure L).

Figure K

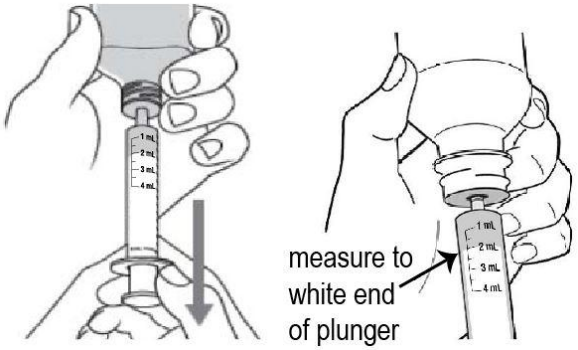
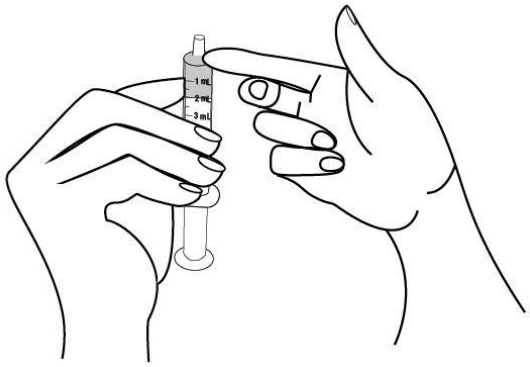


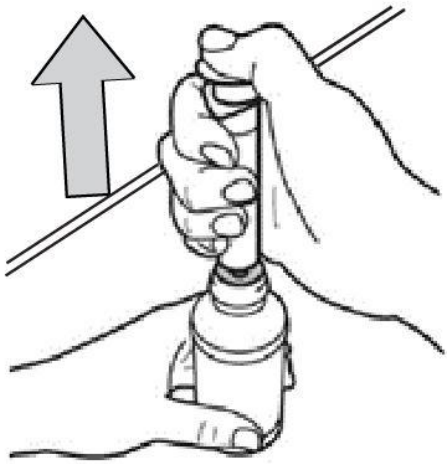
Figure L



Step 8:

- Turn the bottle over and place it upright on a table or countertop, then remove the oral dosing syringe from the bottle adapter (see Figure M).

Figure M



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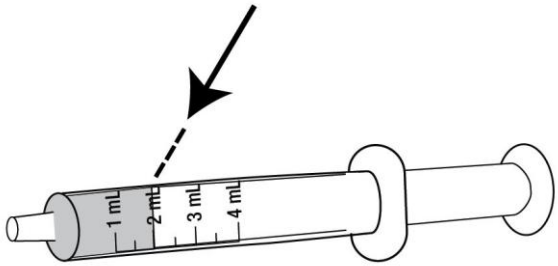
Step 9:

- Check that the correct dose in mL was pulled up into the oral dosing syringe (see Figure N).
- If the dose is not correct:
  - Insert the oral syringe tip back into the bottle and fully push in the plunger to the bottom of the syringe barrel so that all of the oral suspension flows back into the bottle.
  - Repeat Steps 6 through 8.

Figure N



Step 10:

Taking the dose of ONYDA XR:

- The child should be in a seated position before taking ONYDA XR.
- Tilt the head slightly upwards.
- Place the oral dosing syringe into the mouth and point it toward the cheek (see Figure O).
- Close the mouth tightly around the oral dosing syringe and slowly push the plunger all the way down to give the ONYDA XR dose (see Figure P).
- After all the medication has been taken, remove the oral dosing syringe from the mouth.

Figure O

Figure P

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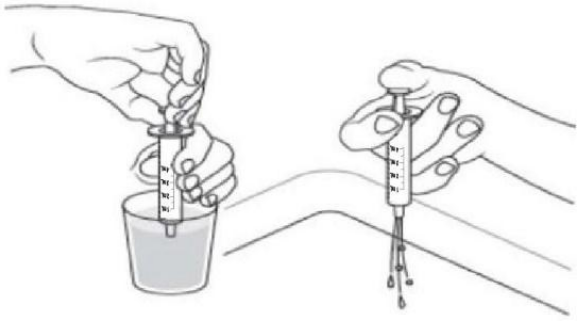
Step 11: **Closing the bottle:** • Put the ONYDA XR cap back on the bottle and close the cap tightly by turning the cap clockwise (see Figure Q).	Figure Q 
Step 12: **Cleaning up:** • Clean the oral dosing syringe after each use by rinsing with tap water (see Figure R). • Allow the oral dosing syringe to dry and keep it in a safe place for the next use. • Wash and dry your hands.	Figure R 

Disposing of ONYDA XR:

- Throw away any unused or expired ONYDA XR in your household trash.
- For the bottles of 30 mL and 60 mL, throw away (discard of) any remaining ONYDA XR if you have not used it 30 days after first opening the bottle.
- For the 120 mL bottle, throw away (discard of) any remaining ONYDA XR if you have not used it 60 days after first opening the bottle.

Storing ONYDA XR:

- Store ONYDA XR at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect from light and keep ONYDA XR in the original container. Tightly close the child-resistant cap.

Keep ONYDA XR and all medicines out of the reach of children.

Manufactured by/Distributed by:
Tris Pharma, Inc.
Monmouth Junction, NJ 08852
Rev. 03

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This Instructions for Use has been approved by the U.S. Food and Drug Administration
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