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----------

Indications and Usage (1)	09/2025
Warnings and Precautions (5.5)	09/2025

----------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)

Limitations of Use
The use of DYANAVEL 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 (5.5, 8.4).

----------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.

Revised: 09/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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)]*.

Limitations of Use

The use of DYANAVEL 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 (5.5), Use in Specific Populations (8.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating patients with DYANAVEL XR, assess:

- for the presence of cardiac disease (i.e., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) *[see Warnings and Precautions (5.2)]*.
- the family history and clinically evaluate patients for motor or verbal tics or Tourette's syndrome before initiating DYANAVEL XR *[see Warnings and Precautions (5.8)]*.

2.2 Recommended Dosage

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

2.3 Administration Information

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

DYANAVEL XR Extended-Release Oral Suspension
Instruct patients to read the "Instructions for Use" for complete administration instructions.

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

DYANAVEL XR Extended-Release Tablets

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

2.4 Switching from Other Amphetamine Products

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

If switching from other amphetamine products, discontinue that treatment, and titrate with DYANAVEL XR using the above titration schedule. Do not substitute for other amphetamine products on a milligram-per-milligram basis, because of different amphetamine salt compositions and differing pharmacokinetic profiles *[*see *Description (11), Clinical Pharmacology (12.3)]*.

2.5 Dosage Modifications due to Drug Interactions

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

3 DOSAGE FORMS AND STRENGTHS

DYANAVEL XR (amphetamine) extended-release oral suspension:

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

DYANAVEL XR (amphetamine) extended-release tablets:

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

All strengths are expressed in terms of amphetamine base equivalents.

4 CONTRAINDICATIONS

DYANAVEL XR is contraindicated:

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

5 WARNINGS AND PRECAUTIONS

5.1 Abuse, Misuse, and Addiction

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

Before prescribing DYANAVEL XR, assess each patient’s risk for abuse, misuse, and addiction. Educate patients and their families about these risks and proper disposal of any unused drug. Advise patients to store DYANAVEL XR in a safe place, preferably locked, and instruct patients to not give DYANAVEL XR

to anyone else. Throughout DYANAVEL XR treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

5.2 Risks for Patients with Serious Cardiac Disease

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

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

5.3 Increased Blood Pressure and Heart Rate

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

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

5.4 Psychiatric Adverse Reactions

Exacerbation of Pre-existing Psychosis

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

Induction of a Manic Episode in Patients with Bipolar Disease

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

New Psychotic or Manic Symptoms

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

5.5 Long-Term Suppression of Growth in Pediatric Patients

DYANAVEL 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. Closely monitor growth (weight and height) in DYANAVEL XR treated pediatric patients treated with CNS stimulants.

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

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

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

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

5.7 Serotonin Syndrome

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

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

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

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

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

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

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

6 ADVERSE REACTIONS

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

- Abuse, Misuse, and Addiction *[*see *Boxed Warning, Warnings and Precautions (5.1),* and *Drug Abuse and Dependence (9.2, 9.3)]*
- Hypersensitivity to amphetamine, or other components of DYANAVEL XR *[*see *Contraindications (4)]*
- Hypertensive Crisis When Used Concomitantly with Monoamine Oxidase Inhibitors *[*see *Contraindications (4)* and *Drug Interactions (7.1)]*
- Risks to Patients with Serious Cardiac Disease *[*see *Warnings and Precautions (5.2)]*
- Increased Blood Pressure and Heart Rate *[*see *Warnings and Precautions (5.3)]*
- Psychiatric Adverse Reactions *[*see *Warnings and Precautions (5.4)]*
- Long-Term Suppression of Growth in Pediatric Patients *[*see *Warnings and Precautions (5.5)]*
- Peripheral Vasculopathy, including Raynaud's phenomenon *[*see *Warnings and Precautions (5.6)]*
- Serotonin Syndrome *[*see *Warnings and Precautions (5.7)]*
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

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

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

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

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

Eye Disorders: Vision blurred, mydriasis.

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

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

Endocrine: Impotence, changes in libido.

Skin: Alopecia.

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

There is limited experience with DYANAVEL XR in controlled trials. Based on this limited experience, the adverse reaction profile of DYANAVEL XR appears similar to other amphetamine extended-release products. The most common (≥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

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	
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.

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 of DYANAVEL XR have not been established in pediatric patients below the age of 6 years.

In studies evaluating extended-release amphetamine products, patients 4 to <6 years of age had higher systemic amphetamine 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 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)]*.

Long-Term Growth Suppression

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

8.5 Geriatric Use

DYANAVEL XR has not been studied in the geriatric population.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

DYANAVEL XR contains amphetamine, a Schedule II controlled substance.

9.2 Abuse

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

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

Misuse and abuse of amphetamine may cause increased heart rate, respiratory rate, or blood pressure; sweating; dilated pupils; hyperactivity; restlessness; insomnia; decreased appetite; loss of coordination;

tremors; flushed skin; vomiting; and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including DYANAVEL XR, can result in overdose and death *[see Overdosage (10)],* and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

9.3 Dependence

Physical Dependence

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

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

Tolerance

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

10 OVERDOSAGE

Clinical Effects of Overdose

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

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

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

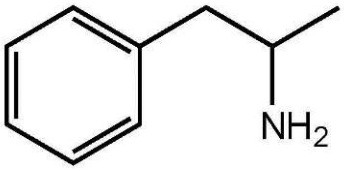
11 DESCRIPTION

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

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

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

Structural Formula:



$C_9H_{13}N$ 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

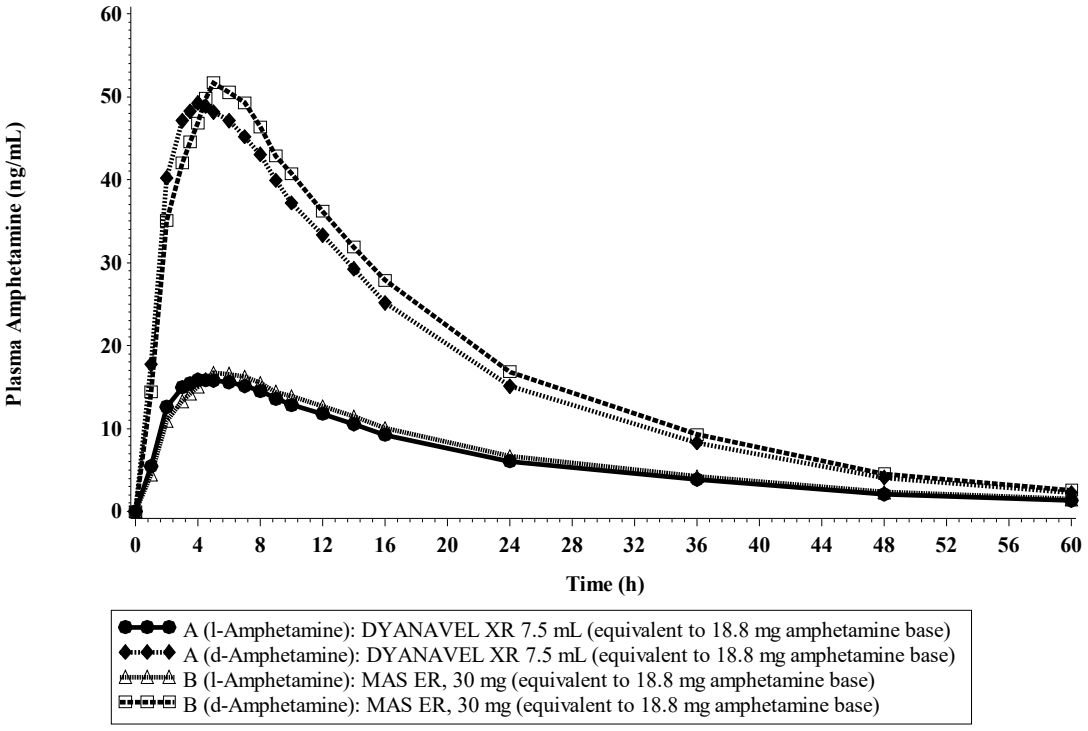
Absorption

Extended-Release Oral Suspension

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

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

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

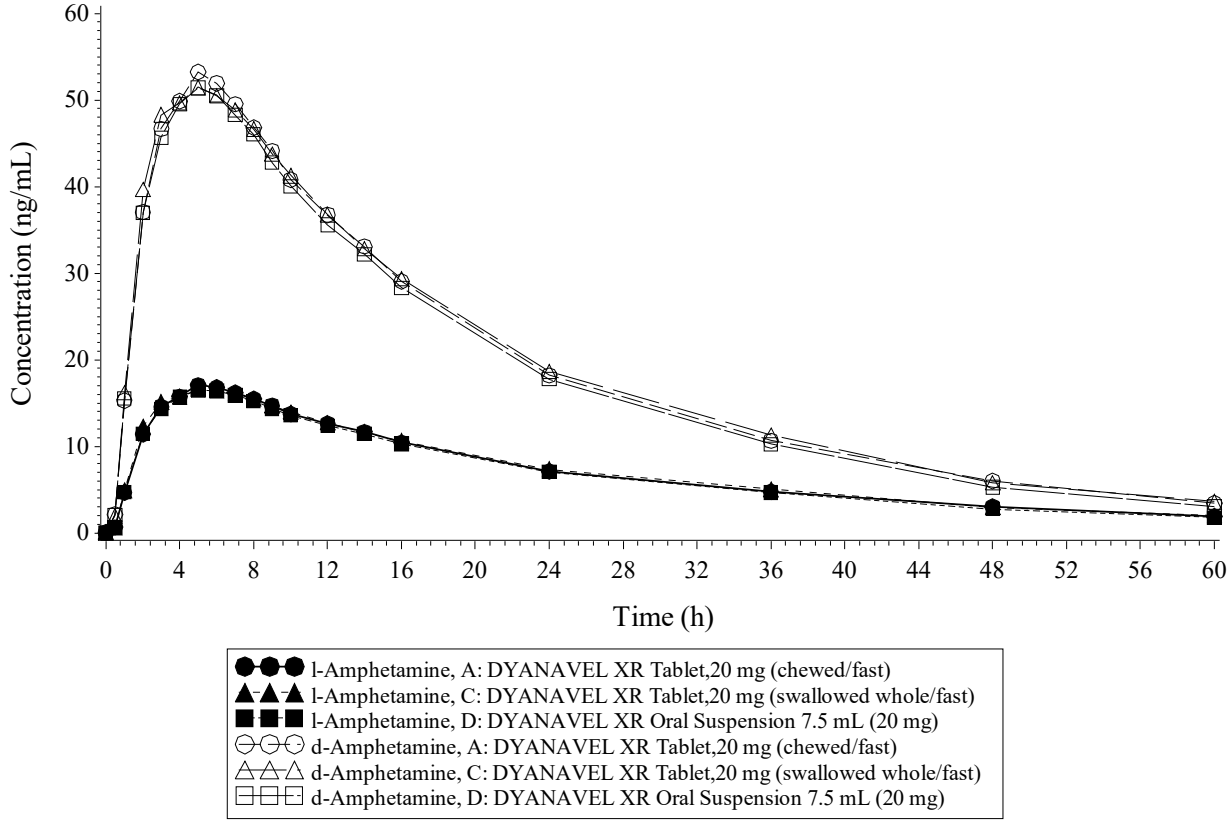


Extended-Release Tablet

Following a single 20 mg dose of DYANAVEL XR extended-release tablets (swallowed whole) to 36 healthy adults under fasted conditions in a crossover study, the median (range) time to peak plasma concentration (T_{max}) for both *d*- and *l*-amphetamine, were 5.0 (2 to 9) hours after dosing. Peak concentrations (C_{max}) for both *d*- and *l*-amphetamine, were 101% of the C_{max} of DYANAVEL XR oral suspension. The relative bioavailability of DYANAVEL XR tablets compared with an equal dose of DYANAVEL XR oral suspension, for *d*- and *l*-amphetamine, were 105% and 106%, respectively.

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

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



Effect of Food

Extended-Release Oral Suspension

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

Extended-Release Tablet

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

Elimination

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

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

Metabolism

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

Excretion

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

Specific Populations

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

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

Drug Interaction Studies

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

Urine pH Modulators
Because amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates. Alkaline urine pH results in less ionization and reduced renal elimination; acidic pH and high flow rates result in increased renal elimination with clearances greater than glomerular filtration rates, indicating the involvement of active secretion. In addition, any decrease in amphetamine's

metabolism that might occur due to drug interactions or genetic polymorphisms is more likely to be clinically significant when renal elimination is decreased *[*see *Drug Interactions (7.1)]*.

Alcohol Effect
There is no *in vivo* study conducted for the effect of alcohol on drug exposure. An *in vitro* dissolution study on DYANAVEL XR extended-release oral suspension showed alcohol-induced dose dumping potential in the presence of 40% alcohol. A similar study on the DYANAVEL XR extended-release tablets showed no alcohol-induced dose dumping in the presence of 40% alcohol. Dose dumping was not observed in the presence of 5%, 10%, or 20% alcohol concentrations for either product.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

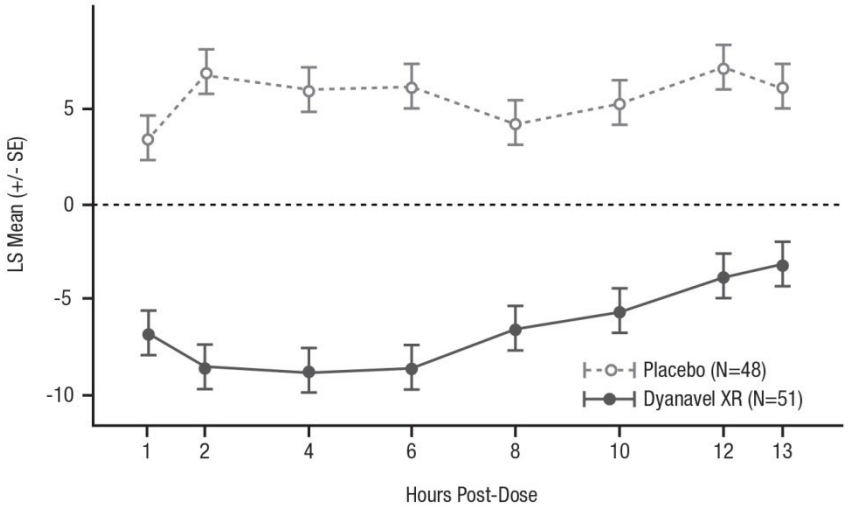
SKAMP-Combined change scores from pre-dose demonstrated a statistically significant improvement at all time points (1, 2, 4, 6, 8, 10, 12, 13 hours) post-dosing with DYANAVEL XR compared to placebo.

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 60 mL (NDC 24478-102-02) and 464 mL (NDC 24478-102-01).

The product is provided in a carton.

60 mL carton contains two oral dispensers and two bottle adapters.

464 mL carton also contains four oral dispensers and four bottle adapters.

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

- 5 mg DYANAVEL XR extended-release tablet is functionally scored and is available as an off-white, speckled, caplet shaped tablet with 5 debossed on one side and scored on the other side, supplied in bottles of 30 (NDC 24478-106-01).
- 10 mg DYANAVEL XR extended-release tablet is available as an off-white, speckled, diamond shaped tablet with 10 debossed on one side and plain on the other side, supplied in bottles of 30 (NDC 24478-108-01).
- 15 mg DYANAVEL XR extended-release tablet is available as an off-white, speckled, triangle shaped tablet with 15 debossed on one side and plain on the other side, supplied in bottles of 30 (NDC 24478-109-01).
- 20 mg DYANAVEL XR extended-release tablet is available as an off-white, speckled, oval shaped tablet with 20 debossed on one side and plain on the other side, supplied in bottles of 30 (NDC 24478-110-01).

Storage and Handling

Dispense in a tight, light-resistant 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

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

Circulation Problems in Fingers and Toes *[*Peripheral vasculopathy, including Raynaud's phenomenon*]*

Instruct patients and their caregivers beginning treatment with DYANAVEL XR about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change color from pale, to blue, to red.

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

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

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

Serotonin Syndrome

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

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

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

Concomitant Medications

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

Pregnancy Registry

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

Pregnancy

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

Lactation

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

Alcohol

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

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

LB8684
Rev. 04

MEDICATION GUIDE

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

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

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

DYANAVEL XR may cause serious side effects, including:

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

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

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

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

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

What is DYANAVEL XR?

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

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

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

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?

- **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.

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.

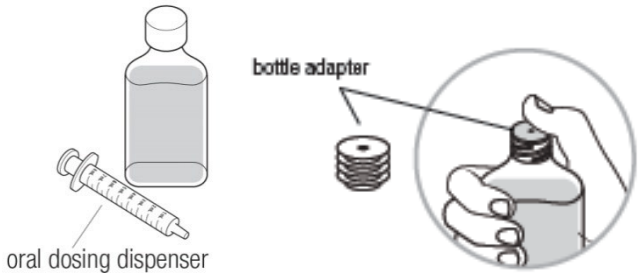
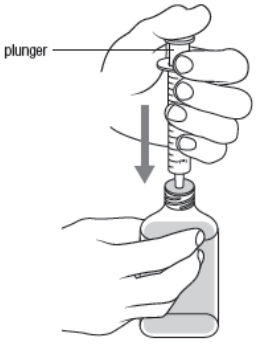
Manufactured by: Tris Pharma, Inc., Monmouth Junction, NJ 08852

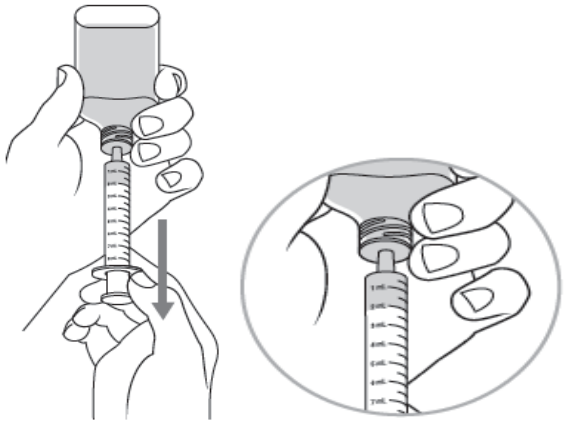
For more information about DYANAVEL XR go to www.dyanavelxr.com or call 1-732-940-0358.

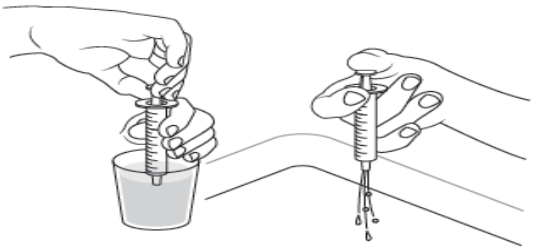
This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 09/2025

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.	

Step 6: • With the oral dosing dispenser in place, hold the DYANAVEL XR bottle with 1 hand and turn the bottle upside down. Pull the plunger down until the white end of the plunger reaches the number of mLs you need for the prescribed dose.	
Step 7: • Turn the bottle over and place upright on a counter top, then remove the oral dosing dispenser from the bottle adapter.	
Step 8: • Place the tip of the oral dosing dispenser into you or your child's mouth. Point the tip toward the cheek and slowly push the plunger all the way down to give the DYANAVEL XR dose.	
Step 9: • Put the DYANAVEL XR cap back on the bottle and close tightly.	

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

How should I store DYANAVEL XR?

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- 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.

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Manufactured by:
Tris Pharma, Inc.
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For more information about DYANAVEL XR go to www.dyanavelxr.com or call 1-732-940-0358.

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Revised: 10/2023