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

Initial U.S. Approval: 1960

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- **CNS stimulants, including DYANAVEL XR, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence (5.1, 9.3)**
- **Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy (9.2, 9.3)**

----------RECENT MAJOR CHANGES----------

Contraindications (4)	**1/2017**
Warnings and Precautions (5.7)	**1/2017**

----------INDICATIONS AND USAGE----------

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

----------DOSAGE AND ADMINISTRATION----------

- Before administering the dose, shake bottle (2.2)
- May be taken with or without food (2.2)
- In children 6 years of age and older, recommended starting dose 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 until optimal response is obtained (2.2)
- Daily dose above 20 mg is not recommended (2.2)
- Do not substitute for other amphetamine products on a milligram-per-milligram basis, because of different amphetamine base compositions and differing pharmacokinetic profiles (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Extended-release oral suspension containing 2.5 mg amphetamine base per mL (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----------

- *Serious Cardiovascular Reactions:* Sudden death has been reported in association with CNS stimulant treatment at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease (5.2)
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic (5.3)
- *Psychiatric Adverse Reactions:* May cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use (5.4)
- *Long-Term Suppression of Growth:* Monitor height and weight in pediatric patients during treatment (5.5)
- *Peripheral Vasculopathy, including Raynaud's phenomenon:* Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants (5.6)
- *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, 17).

----------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. 1-732-940-0358 and www.trispharma.com 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 (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: 1/2017

FULL PRESCRIBING INFORMATION CONTENTS*

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

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ABUSE AND DEPENDENCE

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

1. INDICATIONS AND USAGE

DYANAVEL XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) [see *Clinical Studies (14)*].

2. DOSAGE AND ADMINISTRATION

2.1 Important Information Prior to Initiating Treatment

Prior to treating children, adolescents, and adults with CNS stimulants, including 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)*].

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

2.2 General Dosing Information

DYANAVEL XR should be orally administered once daily in the morning with or without food. The dose should be individualized according to the needs and responses of the patient. Before administering the dose, shake the bottle of DYANAVEL XR.

In children 6 years of age and older, start with 2.5 mg or 5 mg once daily in the morning. The dose may be increased in increments of 2.5 mg to 10 mg per day every 4 to 7 days up to a maximum dose of 20 mg per day.

Pharmacological treatment of ADHD may be needed for extended periods. Healthcare providers should periodically re-evaluate the long-term use of DYANAVEL XR, and adjust dosage as needed.

2.3 Switching from other Amphetamine Products

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 base compositions and differing pharmacokinetic profiles [see *Description (11), Clinical Pharmacology (12.3)*].

2.4 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

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

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 Potential for Abuse and Dependence

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

5.2 Serious Cardiovascular Reactions

Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in children and adolescents with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during DYANAVEL XR treatment.

5.3 Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for potential tachycardia and hypertension.

5.4 Psychiatric Adverse Reactions

Exacerbation of Preexisting Psychosis

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

Induction of a Manic Episode in Patients with Bipolar Illness

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

New Psychotic or Manic Symptoms

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

5.5 Long-Term Suppression of Growth

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

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

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, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

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)*]. Amphetamines and amphetamine derivatives are known to be metabolized, to some degree, by cytochrome P450 2D6 (CYP2D6) *[see Clinical Pharmacology 12.3]*. The potential for a pharmacokinetic interaction exists with the co-administration of CYP2D6 inhibitors which may increase the risk of serotonin syndrome 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)*].

If symptoms of serotonin syndrome occur, discontinue all serotonergic agents immediately, 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.

6. ADVERSE REACTIONS

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

- Drug Dependence [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)*]
- Serious Cardiovascular Reactions [see *Warnings and Precautions (5.2)*]
- Blood Pressure and Heart Rate Increases [see *Warnings and Precautions (5.3)*]
- Psychiatric Adverse Reactions [see *Warnings and Precautions (5.4)*]
- Long-Term Suppression of Growth [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)]

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 clinical practice.

Clinical Trials Experience 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.

Clinical Trials Experience 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 in 108 patients with ADHD (aged 6–12 years) were: epistaxis, allergic rhinitis and upper abdominal pain.

Table 1. Common adverse reactions occurring in ≥2% of Subjects on DYANAVEL XR 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.

Endocrine: frequent or prolonged erections.

Musculoskeletal, Connective Tissue, and Bone Disorders: rhabdomyolysis.

Psychiatric Disorders: dermatillomania.

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:	Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection,

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