

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208147Orig1s000

LABELING

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)

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 (2.1)
- May be taken with or without food (2.1)
- In children 6 years of age and older, recommended starting dose is 2.5 mg or 5 mg once daily in the morning (2.1)
- 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 (2.1)
- Daily dose above 20 mg is not recommended (2.1).
- Do not substitute for other amphetamine products on a milligram-per-milligram basis, because of different amphetamine base compositions and differing pharmacokinetic profiles (2.2)

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)

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: 10/2015

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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)].
- During treatment with MAOIs, and also within 14 days of following discontinuation of treatment with a MAOI, because of the risk of hypertensive crisis [see *Drug Interactions* (7)].

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.

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)*]

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)
<i>Respiratory, thoracic and mediastinal disorders</i>		

Epistaxis	3.8%	0%
Rhinitis allergic	3.8%	0%
<i>Gastrointestinal disorders</i>		
Abdominal pain upper	3.8%	2.1%

6.2 Postmarketing Experience

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

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.

<i>MAO Inhibitors (MAOI)</i>	
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 during or within 14 days following the administration of MAOI [see <i>Contraindications (4)</i>].
Examples	selegiline, isocarboxazid, phenelzine, tranylcypromine
<i>Alkalinizing Agents</i>	
Clinical Impact	Increase blood levels and potentiate the action of amphetamine.
Intervention	Co-administration of DYANAVEL XR and gastrointestinal alkalinizing agents should be avoided.
Examples	Gastrointestinal alkalinizing agents (e.g., sodium bicarbonate). Urinary alkalinizing agents (e.g. acetazolamide, some thiazides).
<i>Acidifying Agents</i>	
Clinical Impact	Lower blood levels and efficacy of amphetamines.
Intervention	Increase dose based on clinical response.
Examples	Gastrointestinal acidifying agents (e.g., guanethidine, reserpine, glutamic acid HCl, ascorbic acid). Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts).
<i>Tricyclic Antidepressants</i>	
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.
Examples	desipramine, protriptyline
Proton Pump Inhibitors	
Clinical Impact	Time to maximum concentration (T_{max}) of amphetamine is increased compared to when administered alone.
Intervention	Monitor patients for changes in clinical effect and adjust therapy based on clinical response.
Example	omeprazole

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

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 1.5 and 8 times, respectively, the maximum recommended human dose (MRHD). However, long-term neurochemical and behavioral effects have been reported in published animal developmental studies using clinically relevant doses of amphetamine (*d*- or *d, l*-) [see [Data](#)]. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

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 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 1.5 and 8 times, respectively, the MRHD of 20 mg/day (as base), on a mg/m^2 body surface area basis for an adolescent. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 times the MRHD) 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

Safety and effectiveness have been established in pediatric patients with ADHD ages 6-17 years [see *Adverse Reactions* (6.1), *Clinical Pharmacology* (12), and *Clinical Studies* (14)]. Safety and efficacy in pediatric patients younger than 6 years with ADHD have not been established.

Long-Term Growth Suppression

Growth should be monitored during treatment with stimulants, including DYANAVEL XR, and children 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, which is a Schedule II controlled substance in the U.S. Controlled Substance Act (CSA).

9.2 Abuse

DYANAVEL XR, is a CNS stimulant that contains amphetamine which has a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.

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

To reduce the abuse of DYANAVEL XR, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and re-evaluate the need for DYANAVEL XR use.

9.3 Dependence

Tolerance

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

Dependence

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

10. OVERDOSAGE

Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdose. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

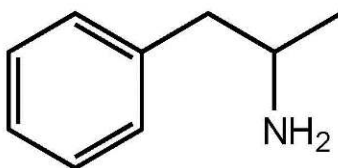
Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Other reactions include arrhythmias, hypertension or hypotension, circulatory collapse, nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

11. DESCRIPTION

DYANAVEL XR (amphetamine) extended release oral suspension, a CNS stimulant, is an extended-release liquid formulation containing a 3.2 to 1 ratio of d- to l-amphetamine.

Each 1 ml of DYANAVEL XR contains 2.5 mg of amphetamine which is the same as the amount of amphetamine (base equivalent) found in a 4 mg strength amphetamine mixed salts product.

Structural Formula:



C₉H₁₃N MW 135.21

DYANAVEL XR utilizes an ion exchange resin where the drug is bound to the resin (sodium polystyrene sulfonate) through an ionic binding reaction. DYANAVEL XR contains immediate release and extended-release components. The extended-release component is coated with an aqueous, pH-independent polymer. After drug release the ion-exchange resin is excreted in the feces.

Inactive Ingredients: anhydrous citric acid, bubblegum flavor, glycerin, methylparaben, modified food starch, polysorbate 80, povidone, polyvinyl acetate, propylparaben, sodium lauryl sulfate, sodium polystyrene sulfonate, sucralose, 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. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

12.3 Pharmacokinetics

Absorption

Following a single, 18.8 mg oral dose of DYANAVEL XR in 29 healthy adult subjects in a crossover study under fasting conditions, d-amphetamine and l-amphetamine, the median (range) time to peak plasma concentrations (T_{max}) were 4.0 (2 – 7) hours after dosing and peak concentration (C_{max}) were 102% and

106%, respectively of the $C_{\max}$ of immediate-release (IR) mixed amphetamine salts tablets. The relative bioavailability of DYANAVEL XR compared to an equal dose of mixed amphetamine salts IR tablets is 106% of d-amphetamine and 111% for l-amphetamine.

Metabolism and Excretion

DYANAVEL XR contains d-amphetamine and l-amphetamine in a ratio of 3.2 to 1. Following a single 18.8 mg oral dose of DYANAVEL XR in 29 healthy adult subjects under fasting conditions, the mean ($\pm$ SD) plasma terminal elimination half-life of d-amphetamine was 12.36 ($\pm$ 2.95 h) hours and the mean ($\pm$ SD) plasma terminal half-life for l-amphetamine was 15.12 ($\pm$ 4.40 h) hours. 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. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

Amphetamine is known to inhibit monoamine oxidase, whereas the ability of amphetamine and its metabolites to inhibit various P450 isozymes and other enzymes has not been adequately elucidated. *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, due to the probability of auto-inhibition and the lack of information on the concentration of these metabolites relative to *in vivo* concentrations, no predictions regarding the potential for amphetamine or its metabolites to inhibit the metabolism of other drugs by CYP isozymes *in vivo* can be made.

With normal urine pHs approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30% to 40% of the dose is recoverable in urine as amphetamine itself. Since amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates. Alkaline urine pHs result in less ionization and reduced renal elimination, and acidic pHs and high flow rates result in increased renal elimination with clearances greater than glomerular filtration rates, indicating the involvement of active secretion. 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. In addition, drugs that affect urinary pH are known to alter the elimination of amphetamine, and 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)].

Food Effect

In a study in adult volunteers to investigate the effects of a high-fat meal on the bioavailability of DYANAVEL XR at a dose of 18.8 mg, the presence of food delayed the time to peak concentration of both d- and l-amphetamine by approximately 1 hour (fed: median [range] 5 [3 – 8] hours vs. fasted: 4 [2 – 7] hours). Overall, a high-fat meal increased the average $C_{\max}$ of both isomers of DYANAVEL XR by about 2% and decreased the AUC by 5-7% (5.7% decrease for d-amphetamine and 7.4% for l-amphetamine). These changes are not considered clinically significant.

Specific Populations

Pediatric

Following a single 10 mg oral dose of DYANAVEL XR in 12 pediatric subjects with ADHD (aged 6-12 years) under fasting conditions, d-amphetamine and l-amphetamine peak plasma concentrations occurred at a median time of 3.9 and 4.5 hours after dosing, respectively. The mean plasma terminal elimination half-life of d-amphetamine was 10.43 ($\pm$ 2.01 h) hours and the mean plasma terminal half-life for l-amphetamine was 12.14 ($\pm$ 3.15 h) hours.

Alcohol Effect

There is no *in vivo* study conducted for the effect of alcohol on drug exposure. An *in vitro* dissolution study showed alcohol-induced dose dumping potential in the presence of 40% alcohol. Dose dumping was not observed in the presence of lower alcohol concentrations.

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 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 20 mg/day (as base) on a mg/m² body surface area basis for a child.

Mutagenesis

Amphetamine, in the enantiomer ratio present in DYANAVEL XR (*d*- to *l*- ratio of 3.2 to 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 present in DYANAVEL XR (*d*- to *l*- ratio of approximately 3.2 to 1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day [approximately 5 times the maximum recommended human dose of 20 mg/day (as base) on a mg/m² body surface area basis for an adolescent].

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 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. Results from the double-blind, placebo-controlled week of the study are summarized in Table 3 and Figure 1.

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.

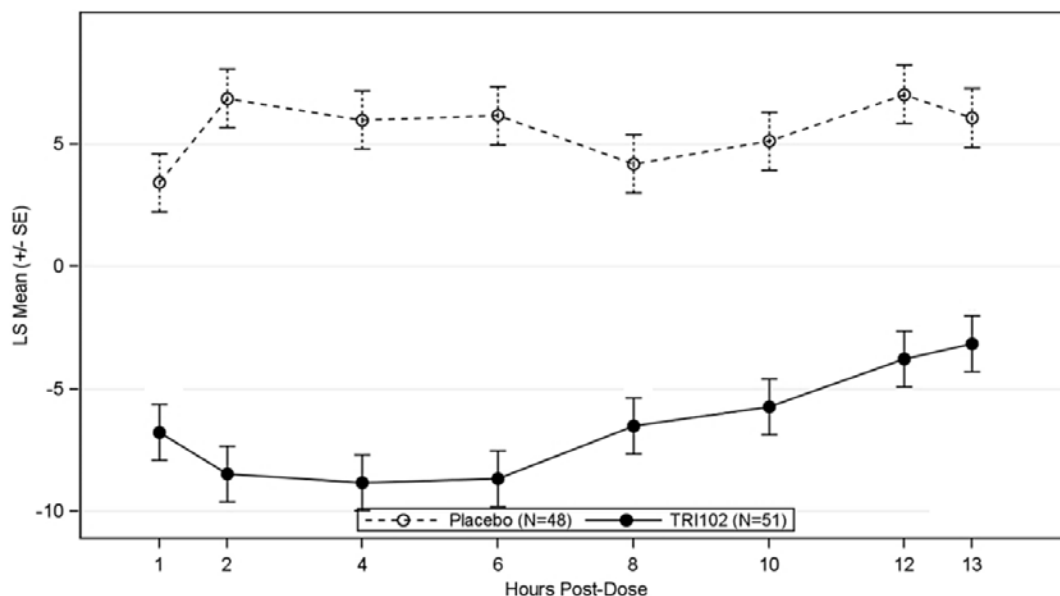
Table 3: Primary efficacy result.

Study Number	Treatment Group	Primary Efficacy Measure: SKAMP-Combined Score		
		Mean Predose Score (SD)	LS Mean Change from Pre-Dose at 4 Hours Post-Dosing (SE)	Placebo-subtracted Difference ^a (95% CI)
Study 1	DYANAVEL XR	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 1. Change from pre-dose in SKAMP-Combined Score after treatment with DYANAVEL XR or Placebo.



16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DYANAVEL XR (amphetamine) extended-release oral suspension, the concentration is 2.5 mg/mL amphetamine base and is supplied as light beige to tan viscous suspension with bubblegum flavor in bottles of 464 mL (NDC 27808-102-01).

16.2 Storage and Handling

Dispense in a tight container with child-resistant closure.

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

The pharmacist should provide an oral dosing syringe or other suitable measuring device.

Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired DYANAVEL XR at authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or authorized collector is available, mix DYANAVEL XR with an undesirable, nontoxic substance to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and discard DYANAVEL XR in the household trash.

17. PATIENT COUNSELING INFORMATION

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

Controlled Substance Status/Potential for Abuse, Misuse, and Dependence

Advise patients that DYANAVEL XR is a federally controlled substance because it can be abused or lead to dependence. Advise patients to store DYANAVEL XR in a safe place, preferably locked, to prevent abuse. Advise patients to comply with laws and regulations on drug disposal. Advise patients to dispose of remaining, unused, or expired DYANAVEL XR by a medicine take-back program if available [see *Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9)*].

Dosage and Administration Instructions

Provide the following instructions on administration to the patient:

- Use with an oral dosing device or other suitable measuring device
- Shake the bottle of DYANAVEL XR before each dose.
- Measure the appropriate dose as prescribed by the physician.
- Using the filled oral dosing syringe or measuring device, dispense DYANAVEL XR directly into mouth.
- Replace bottle cap and store bottle as directed.
- Wash oral dosing syringe or measuring device after each use.

Serious Cardiovascular Risks

Advise patients of serious cardiovascular risk (including sudden death, myocardial infarction, stroke, and hypertension) with DYANAVEL XR. 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)*].

Blood Pressure and Heart Rate Increases

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

Psychiatric Risks

Advise patients 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

Advise patients 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 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 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 DYANAVEL XR.

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

Pregnancy

Advise patients 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

Patients should be advised 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)].

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

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

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

Tell your doctor if you or your child has ever abused or been dependent on alcohol, prescription medicines, or street drugs.

DYANAVEL XR is a stimulant medicine. Some patients have had the following problems when taking stimulant medicines such as DYANAVEL XR.

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

1. Heart-related problems:

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

Tell your doctor if you or your child has any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your doctor should check you or your child carefully for heart problems before starting DYANAVEL XR.

Your doctor should check your or your child's blood pressure and heart rate regularly during treatment with DYANAVEL XR.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking DYANAVEL XR.

2. Mental (Psychiatric) problems:

All Patients

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

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

Call your doctor right away if you have or your child has any new or worsening mental symptoms or problems while taking DYANAVEL XR, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

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

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

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

Call your doctor right away if you have or your child has any signs of unexplained wounds appearing on fingers or toes while taking DYANAVEL XR.

What is DYANAVEL XR?

DYANAVEL XR is a central nervous system stimulant prescription medicine. **It is used for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD).** DYANAVEL XR may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

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

Who should not take DYANAVEL XR?

DYANAVEL XR should not be taken if you or your child:

- **are allergic to amphetamine, or any of the ingredients in DYANAVEL XR. See the end of this Medication Guide for a complete list of ingredients in DYANAVEL XR.**
- **are taking or have taken within the past 14 days an anti-depression medicine called monoamine oxidase inhibitor or MAOI.**

What should I tell my doctor before taking DYANAVEL XR?

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

- heart problems, heart defects, or high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- circulation problems in fingers and toes

Tell your doctor:

- if you or your child have any kidney problems. Your doctor may lower the dose.
- if you are or your child is pregnant, or plan to become pregnant. It is not known if DYANAVEL XR will harm your unborn baby.
- If you are or your child is breastfeeding or plan to breastfeed. DYANAVEL XR passes into breast milk. Discuss with your doctor before you breastfeed while you are taking DYANAVEL XR.

Tell your doctor 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 while taking DYANAVEL XR.

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

Especially tell your doctor if you or your child takes:

- anti-depression medicines including MAOIs

Know the medicines that you or your child take. Keep a list of your medicines with you to show your doctor and pharmacist.

Do not start any new medicine while taking DYANAVEL XR without talking to your doctor first.

How should DYANAVEL XR be taken?

- **Take DYANAVEL XR exactly as prescribed.** Your doctor may adjust the dose until it is right for you or your child.
- Take DYANAVEL XR oral suspension 1 time each day in the morning.
- DYANAVEL XR can be taken with or without food.
- Shake the DYANAVEL XR bottle well before you use it.
- Use an oral dosing syringe or other measuring device to help you measure the right amount of DYANAVEL XR.
- Your doctor may sometimes stop DYANAVEL XR treatment for a while to check your ADHD symptoms.
- Your doctor may do regular checks of your or your child's blood, heart, and blood pressure while taking DYANAVEL XR.
- Children should have their height and weight checked often while taking DYANAVEL XR. DYANAVEL XR treatment may be stopped if a problem is found during these check-ups.
- **If you or your child take(s) too much DYANAVEL XR, call your doctor or poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.**

What should I avoid while taking DYANAVEL XR?

- drinking alcohol

What are possible side effects of DYANAVEL XR?

DYANAVEL XR can cause serious side effects, including:

- See “**What is the most important information I should know about DYANAVEL XR?**” for information on reported heart and mental problems.
- slowing of growth (height and weight) in children

Common side effects of amphetamine products include:

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

Talk to your doctor if you or your child have any side effects that bother you or do not go away.

These are not all the possible side effects of DYANAVEL XR. Ask your doctor or pharmacist for more information.

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 authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or 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.**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 condition. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about DYANAVEL XR. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about DYANAVEL XR that was written for healthcare professionals.

For more information about DYANAVEL XR please contact Tris Pharma at 1-732-940-0358 or www.trispharma.com.

What is the ingredient in DYANAVEL XR?

Active Ingredient: amphetamine.

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

Manufactured by: **Tris Pharma, Inc.** Monmouth Junction, NJ 08852 www.trispharma.com

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

Rev. XX/XXXX



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/s/

MITCHELL V Mathis
10/19/2015