Product Monograph

Including Patient Medication Information

DYANAVEL® XR

amphetamine extended-release oral suspension

For oral use

2.5 mg / mL amphetamine

(as amphetamine [complexed with sodium polystyrene sulfonate], dextroamphetamine sulfate, and amphetamine aspartate)

amphetamine extended-release tablets

For oral use

5 mg, 10 mg, 15 mg, 20 mg amphetamine

(as amphetamine [complexed with sodium polystyrene sulfonate], dextroamphetamine sulfate, and amphetamine aspartate)

Central Nervous System Stimulant

Kye Pharmaceuticals Inc.
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L5N 2X7

Date of Authorization:
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Recent Major Label Changes

Not applicable

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

DYANAVEL XR (amphetamine extended-release oral suspension and amphetamine extended-release tablets) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in:

- Children (6 – 12 years of age)
- Adults (18 years of age and older)

Need for Comprehensive Treatment Program

DYANAVEL XR is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Drug treatment is not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential in children and adolescents with this diagnosis and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Long-Term Use

The effectiveness of DYANAVEL XR for long-term use, i.e., for more than 7 weeks in children aged 6 to 12 years and more than 5 weeks in adults, has not been systematically evaluated in controlled trials. Therefore, the healthcare professional who elects to use DYANAVEL XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see 4 Dosage and Administration).

1.1. Pediatrics

Pediatrics (< 6 years of age): DYANAVEL XR should not be used in children under six years. The safety and effectiveness of DYANAVEL XR in pediatric patients less than 6 years of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use in patients under 6 years of age.

Pediatrics (6-12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of DYANAVEL XR in pediatric patients (6-12 years of age) have been established. Therefore, Health Canada has authorized an indication for pediatric use (see 4.2. Recommended Dose and Dosage Adjustment).

Adolescents (13 – 17 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of DYANAVEL XR in pediatric patients aged 13-17 years have not been established; therefore, Health Canada has not authorized an indication for use in ages 13-17 years (see 7.1.3 Pediatrics).

1.2. Geriatrics

Geriatrics (≥ 65 years of age): DYANAVEL XR has not been studied in the geriatric population. Consideration should be given to hepatic, renal and cardiovascular function prior to prescribing (see 4.2 Recommended Dose and Dosage Adjustment and 7.1.4 Geriatrics).

2. Contraindications

DYANAVEL XR is contraindicated in patients:

- who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition and Packaging.
- with a known hypersensitivity or idiosyncrasy to the sympathomimetic amines
- with thyrotoxicosis
- with advanced arteriosclerosis
- with symptomatic cardiovascular disease
- with hyperthyroidism
- with moderate to severe hypertension
- with glaucoma
- with agitated states
- with history of drug abuse
- undergoing concomitant treatment with monoamine oxidase inhibitors (MAOIs) or within 14 days following the withdrawal of MAOIs (hypertensive crises may result) (see 9.4 Drug-Drug Interactions).
- allergic to amphetamine
- with pheochromocytoma

3. Serious Warnings and Precautions Box

Misuse and Serious Cardiovascular Adverse Events

- Like other stimulants DYANAVEL XR has the potential for abuse, misuse, dependence or diversion for non-therapeutic uses that healthcare professionals should consider when prescribing this product (see 7 Warnings and Precautions, Dependence, Tolerance and/or Abuse Liability).
- The misuse of amphetamines may cause serious cardiovascular adverse events and sudden death (see 7 Warnings and Precautions, Cardiovascular, Misuse and Serious Cardiovascular Adverse Events).

4. Dosage and Administration

4.1. Dosing Considerations

- DYANAVEL XR is to be administered orally in the morning. Dosage should be individualized according to the needs and response of the patient.
- DYANAVEL XR should be administered starting at the lowest possible dose. Dosage should then be individually and slowly adjusted to the lowest effective dose since individual patient response to DYANAVEL XR varies widely (see 4.2 Recommended Dose and Dosage Adjustment).
- The effect of renal impairment on the pharmacokinetics of DYANAVEL XR has not been assessed as d-amphetamine is not dialyzable. In patients with severe renal impairment (GFR 15 to <30 mL/min/1.73m^2) the recommended dosage should be reduced and the maximum dosage not

exceeded (see 10.3 Pharmacokinetics, Special Populations and Conditions; 7 Warnings and Precautions, Renal).

- DYANAVEL XR should not be used in patients with symptomatic cardiovascular disease and should generally not be used in patients with known structural cardiac abnormalities (see 2 Contraindications and 7 Warnings and Precautions, Cardiovascular).
- Theoretically, there exists a pharmacological potential for all ADHD medications to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.
- Prior to treating children with CNS stimulants including DYANAVEL XR, assess for the presence and familial history of cardiac disease, arrhythmias and sudden death (see 7 Warnings and Precautions, Cardiovascular).
- Assess the patient history of substance use prior to prescribing and monitor for signs of abuse and dependence, while on therapy. Maintain careful prescription records, educate patients about amphetamine abuse potential, monitor for signs of overuse, and periodically re-evaluate the need for DYANAVEL XR use (see 3 Serious Warnings and Precautions Box, 7 Warnings and Precautions).
- Patients should be advised to avoid alcohol while taking DYANAVEL XR (see 9.3 Drug-Behaviour Interactions).
- Careful clinical evaluation for motor or verbal tics of Tourette's syndrome should be conducted before initiating DYANAVEL XR (see 7 Warnings and Precautions, Neurologic, Tics).
- Prior to initiating treatment with a stimulant, 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, and depression) (see 7 Warnings and Precautions, Psychiatric, Screening Patients for Bipolar Disorder).
- Pharmacologic treatment of ADHD may be needed for extended periods. However, healthcare professionals should periodically re-evaluate the long-term use of DYANAVEL XR and adjust dosage as needed. Drug holidays should be considered.
- Patients requiring extended treatment with DYANAVEL XR should undergo periodic evaluation of their cardiovascular status (see 7 Warnings and Precautions, Cardiovascular).

4.2. Recommended Dose and Dosage Adjustment

DYANAVEL XR Tablets and DYANAVEL XR Oral Suspension (children 6-12 years and adults)

- DYANAVEL XR Oral Suspension and DYANAVEL XR Tablets are interchangeable and can be substituted with each other on a milligram per milligram basis (see 10 Clinical Pharmacology).
- DYANAVEL XR is not interchangeable with other amphetamine products. Do not substitute for other amphetamine products on a milligram-per-milligram basis, because of different amphetamine salt compositions and differing pharmacokinetic profiles (see 10 Clinical Pharmacology). If switching from another amphetamine product, discontinue that treatment and titrate with DYANAVEL XR Oral Suspension or DYANAVEL XR Tablets according to the dosing instructions below.
- As with any CNS stimulant, during titration of DYANAVEL XR, the prescribed dose should be adjusted, if necessary, until a well-tolerated, therapeutic dose is achieved.

Renal Insufficiency

- The effect of renal impairment on the pharmacokinetics of DYANAVEL XR has not been assessed; d-amphetamine is not dialyzable. Consequently, renal dysfunction has the potential to inhibit the elimination of amphetamine and result in prolonged exposures. (see 7 Warnings and Precautions, Renal; 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

DYANAVEL XR Tablets

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

DYANAVEL XR Oral Suspension

Pediatrics

- The recommended starting dose is 2.5 to 5 mg (1-2 mL) once daily in the morning. The dose may be increased in increments of 2.5 mg to 5 mg (1-2 mL) per day every 4 to 7 days based on clinical response. The maximum recommended dose is 20 mg (8 mL) once daily.

Adults

- The recommended starting dose is 5 mg (2 mL) once daily in the morning. The dose may be increased in increments of 2.5 to 5 mg (1-2 mL) per day every 4 to 7 days based on clinical response. The maximum recommended dose is 20 mg (8 mL) once daily.

4.2.1. Discontinuing Treatment

Abrupt discontinuation or dose reduction following prolonged use of CNS stimulants, including DYANAVEL XR, may be associated with withdrawal signs and symptoms. These include dysphoric mood, depression, suicidal behaviour or ideation, fatigue, vivid and/or unpleasant dreams, insomnia or hypersomnia, increased appetite, abdominal discomfort and psychomotor retardation or agitation. Careful supervision is therefore recommended during drug withdrawal (see 7 Warnings and Precautions, Dependence, Tolerance and/or Abuse Liability).

4.4. Administration

DYANAVEL XR should be orally administered once daily in the morning with or without food (see 10 Clinical Pharmacology).

The effect of DYANAVEL XR might last into the evening, take as soon as possible in the morning to avoid any potential effect on sleep.

DYANAVEL XR Oral Suspension (children over 6 years and adults):

- Instruct patients to read the “Instructions for Use” provided by their pharmacist for complete administration instructions.
- DYANAVEL XR extended-release oral suspension should be shaken vigorously for at least 10 seconds to ensure that the proper dose is administered.

DYANAVEL XR Tablets (children over 6 years and adults):

- May be chewed or swallowed whole (see 10 Clinical Pharmacology).
- The 5 mg extended-release tablet is functionally scored and may be divided into equal halves (2.5 mg) at the score line.

4.5. Missed Dose

If a dose of DYANAVEL XR is missed, the patient should be instructed to take the next dose in the usual amount at the usual time the next morning. Patients should be instructed not to take an afternoon dose and not to double the dose.

5. Overdose

Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Symptoms: Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, aggression, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Takotsubo cardiomyopathy may develop. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Posterior reversible encephalopathy syndrome (PRES) has been reported in association with amphetamine overdose. Symptoms indicating PRES include headache, altered mental status, seizures and visual disturbances. Diagnosis should be confirmed by radiological procedure (e.g., MRI). If PRES is suspected or diagnosed, appropriate measures should be taken. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae.

Fatal poisoning is usually preceded by convulsions and coma.

Treatment: Treatment of overdose consists of appropriate supportive measures. Consult with a Certified Poison Control Center for up-to-date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit its recommendation in this regard. D- amphetamine is not dialyzable. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amphetamine overdose, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

The prolonged release of amphetamine from DYANAVEL XR should be considered when treating patients with overdose.

The possibility of multiple drug ingestion, including alcohol, should be considered (see 9.3 Drug-Behaviour Interactions).

Animal Toxicology

Administration 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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 - Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Extended-Release for Oral Suspension: 2.5 mg amphetamine base equivalents per mL	Anhydrous citric acid, beta damascone, citral, d-limonene, ethyl acetate, ethyl butyrate, glycerin, isoamyl acetate, iso-amyl butyrate, iso-butyl acetate, methylparaben, modified starch, orange oil, polysorbate 80, polyvinyl acetate, povidone, propylene glycol, propylparaben, sodium lauryl sulfate, sodium polystyrene sulfonate, sucralose, tangerine oil, triacetin, vanillin, and xanthan gum.
Oral	Extended-Release Tablets: 5, 10, 15 and 20 mg amphetamine base equivalents	Citral, crospovidone, d-limonene, ethyl acetate, ethyl alcohol, ethyl butyrate, eugenol, gamma methyl ionone, guar gum, isoamyl acetate, iso-amyl butyrate, iso-butyl acetate, magnesium stearate, mannitol, microcrystalline cellulose, modified corn starch, orange oil, polyvinyl acetate, povidone, silicon dioxide, sodium lauryl sulfate, sodium polystyrene sulfonate, sucralose, talc, tangerine oil, triacetin, vanillin and xanthan gum.

Description

DYANAVEL XR has a tablet and oral suspension formulation that uses a drug delivery technology called LiquiXR® made up of resin bound uncoated immediate release drug and extended-release drug with variable coating. The combination of free drug, resin-bound uncoated drug and resin bound coated drug with variable thickness coating results in continuous release of 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.

DYANAVEL XR (amphetamine) extended-release oral suspension:

- A beige to tan viscous suspension available as 2.5 mg amphetamine base equivalents per mL. Each bottle contains 464 mL of the oral suspension.
- Each carton is packaged with one (1) 16 oz amber bottle, along with four (4) oral dispensers and four (4) LDPE bottle adaptors.
- 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 0.3 mg of amphetamine aspartate and 0.5 mg of dextroamphetamine sulfate).

DYANAVEL XR (amphetamine) extended-release tablets are supplied as follows:

- 5 mg: Off-white, speckled, caplet shaped tablet with '5' debossed on one side and functionally scored on the other side. Available in bottles of 30 tablets each.
- 10 mg: Off-white, speckled, diamond shaped tablet with '10' debossed on one side and plain on the other side. Available in bottles of 30 tablets each.

- 15 mg: Off-white, speckled, triangle shaped tablet with '15' debossed on one side and plain on the other side. Available in bottles of 30 tablets each.
- 20 mg: Off-white, speckled, oval shaped tablet with '20' debossed on one side and plain on the other side. Available in bottles of 30 tablets each.

All strengths are expressed in terms of amphetamine base equivalents.

7. Warnings and Precautions

See 3 Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

- The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdose. DYANAVEL XR should be used with caution in patients who use other sympathomimetic medications.
- All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who:
    - are involved in strenuous exercise or activities,
    - use other sympathomimetic ADHD medications or
    - have a family history of sudden/cardiac death. Prior to the initiation of treatment, a personal and family history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease.

Carcinogenesis and Genotoxicity

See 16 Non-Clinical Toxicology.

Cardiovascular

- **Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems**

  Children and Adolescents

  Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in pediatric patients 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 (see 2 Contraindications).

  Adults

  Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs (see 2 Contraindications).

- **Pre-existing Cardiovascular and Cerebral Vascular Conditions**

  Central Nervous System (CNS) stimulants should be used with caution in patients with a pre-existing cardiovascular or cerebrovascular condition, taking into account risk predictors for these conditions. Patients should be screened for pre-existing or underlying cardiovascular or cerebrovascular conditions before initiation of treatment with stimulants and monitored for new conditions of the heart or brain during the course of treatment.

- **Hypertension and Other Cardiovascular Conditions**

  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) but individuals may have larger increases. Monitor all patients for potential tachycardia and hypertension.

  Blood pressure should be monitored at appropriate intervals in patients receiving stimulants, especially in patients with pre-existing conditions that may result in hypertension.

- **QTc Prolongation**

  Amphetamine has been shown to prolong QTc interval in some patients (see 8.5 Post-Market Adverse Reactions). It should be used with caution in patients with known prolongation of the QTc interval or congenital Long QT syndrome, in patients treated with drugs affecting the QTc interval or in patients with relevant pre-existing cardiac disease or electrolyte disturbances. DYANAVEL XR is contraindicated in patients with symptomatic cardiovascular disease and also in patients with moderate to severe hypertension (see 2 Contraindications).

- **Misuse and Serious Cardiovascular Adverse Events**

  The misuse of central nervous system stimulants may cause serious cardiovascular adverse events and sudden death (see 3 Serious Warnings and Precautions Box).

- **Peripheral Vasculopathy, Including Raynaud's Phenomenon**

  Stimulants used to treat ADHD, including amphetamine products, 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.

Dependence, Tolerance and/or Abuse Liability

Amphetamines have a high potential for abuse (see 3 Serious Warnings and Precautions Box). Tolerance, extreme psychological dependence, and severe social disability have occurred in this context. There are reports of patients who have increased the dosage to levels many times higher than recommended. The smallest possible amount of DYANAVEL XR should be prescribed or dispensed at one time. The possibility of tolerance and psychological dependence, particularly with excessive use, should be kept in mind. Therefore, care should be taken in the selection of patients for DYANAVEL XR therapy, in particular if patients have a previous history of drug or alcohol dependence or substance use disorder.

Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Careful supervision is therefore recommended

during drug withdrawal. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. DYANAVEL XR can be diverted for nontherapeutic use in illicit channels or distribution.

Driving and Operating Machinery

Stimulants may impair the ability of the patient to operate potentially hazardous machinery or vehicles. Patients should be cautioned accordingly until they are reasonably certain that DYANAVEL XR does not adversely affect their ability to engage in such activities.

Endocrine and Metabolism

- **Long-Term Suppression of Growth**

  Long-term suppression of growth has not been evaluated with DYANAVEL XR. In a controlled trial of extended-release amphetamine in adolescents aged 13 to 17 years, mean weight change from baseline within the initial 4 weeks of therapy was –1.1 lbs and –2.8 lbs, respectively, for patients receiving 10 mg and 20 mg extended-release amphetamine. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment. Published data for other stimulants report that in children aged 7-10 years, there is a temporary slowing in growth rate without evidence of growth rebound on treatment. Data are inadequate to determine whether the chronic use of amphetamines in children may be causally associated with suppression of growth.

  While DYANAVEL XR is not indicated in pediatric patients under six years of age, stimulants, including amphetamine, may lead to a greater risk of weight loss and other adverse reactions than in older children taking the same dose of the same medication.

  Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

Monitoring and Laboratory Tests

Periodic laboratory tests are advised during prolonged therapy. The tests should include, but not be limited to, haematological parameters, including complete blood count, differential and platelet counts, and liver enzymes.

Neurologic

- **Tics**

  Amphetamines have been reported to exacerbate motor and phonic tics in Tourette's syndrome. Therefore, careful clinical evaluation for tics in Tourette's syndrome in children and their families should precede use of stimulant medications. DYANAVEL XR has been associated with new onset of tics, though not necessarily associated with Tourette's syndrome.

- **Seizures**

  There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

- **Serotonin toxicity/ serotonin syndrome**

  Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with amphetamines, including DYANAVEL XR, with concomitant use of serotonergic or dopaminergic drugs (see 9.1 Serious Drug Interactions).

  Serotonin toxicity is characterized by neuromuscular excitation, autonomic stimulation (e.g., tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

  - Spontaneous clonus
  - Inducible clonus or ocular clonus with agitation or diaphoresis
  - Tremor and hyperreflexia
  - Hypertonia and body temperature >38°C and ocular clonus or inducible clonus

  If concomitant treatment with DYANAVEL XR and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.1 Serious Drug Interactions). If serotonin toxicity is suspected, discontinuation of DYANAVEL XR and other serotonergic agents should be considered and appropriate treatment instituted.

Ophthalmologic

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment (see 2 Contraindications).

Psychiatric

- **Pre-Existing Psychosis**

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

- **Screening Patients for Bipolar Disorder**

  Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed or manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. Such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

- **Emergence of 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.

- **Aggression, Anxiety and Agitation**

  Patients with an element of agitation may react adversely; discontinue therapy if necessary.

  Aggressive behaviour, marked anxiety, hostility or agitation has been observed in patients with ADHD, and have been reported in clinical trials and the post-marketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behaviour or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behaviour, marked anxiety, hostility or agitation.

- **Suicidal Behaviour and Ideation**

  There have been post-marketing reports of suicide-related events in patients treated with ADHD medications, including cases of ideation, attempts, and very rarely, completed suicide. The mechanism of this risk is not known. ADHD and its related co-morbidities may be associated with increased risk of suicidal ideation and/or behaviour.

  Therefore, it is recommended for patients treated with ADHD medications that caregivers and healthcare professionals monitor for signs of suicide-related behaviour, including at dose initiation/ optimization and drug discontinuation. Patients should be encouraged to report any distressing thoughts or feelings at any time to their healthcare professional. Patients with emergent suicidal ideation and behaviour should be evaluated immediately. The healthcare professional should initiate appropriate treatment of the underlying psychiatric condition and consider a possible change in the ADHD treatment regimen (see 8.5 Post-Market Adverse Reactions).

Renal

The effect of renal impairment on the pharmacokinetics of DYANAVEL XR has not been assessed. d-amphetamine is not dialyzable. In patients with severe renal impairment (GFR 15 to <30 mL/min/1.73m^2) the recommended dosage should be reduced and the maximum dosage not exceeded (see 4.2 Recommended Dose and Dose Adjustment, Renal Insufficiency; 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

Reproductive Health

- **Fertility**

Amphetamine, in the enantiomer 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).

7.1. Special Populations

7.1.1. Pregnancy

Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation and significant lassitude. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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. Long-term neurochemical and behavioral effects have been reported in published animal developmental studies using clinically relevant doses of amphetamine (see 16 Non-Clinical Toxicology, Reproductive and developmental toxicology).

- **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.

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 (see 16 Non-Clinical Toxicology, Reproductive and developmental toxicology).

A number of studies in rodents indicate that prenatal or early postnatal administration of amphetamine (d- or d, l-), at doses which provide similar exposure 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 (see 16 Non-Clinical Toxicology, Reproductive and developmental toxicology).

7.1.2. Breastfeeding

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 dose 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, breastfeeding is not recommended during treatment with DYANAVEL XR.

7.1.3. Pediatrics

Pediatrics (<6 years of age): DYANAVEL XR should not be used in children under six years. Based on the data submitted and reviewed by Health Canada, the safety and efficacy of DYANAVEL XR in pediatric patients under age 6 have not been established; therefore, Health Canada has not authorized an indication for pediatric use. Particular caution is warranted in this population due to a greater risk of weight loss (see 7 Warnings and Precautions, Endocrine and Metabolism).

Adolescents (13 – 17 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of DYANAVEL XR in pediatric patients aged 13-17 years have not been established; therefore, Health Canada has not authorized an indication for use in this age range. Pharmacometric modeling data suggests that the projected pharmacokinetic profile of DYANAVEL XR in adolescents matches closely to that observed in children and adults.

7.1.4. Geriatrics

DYANAVEL XR has not been studied in patients 65 years of age and older (see 1.2 Geriatrics). In general, dose selection for a geriatric patient should be cautious, usually starting at the low end of the dosing

range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy.

8. Adverse Reactions

8.1. Adverse Reaction Overview

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. In a single clinical trial with DYANAVEL XR Oral Suspension, the most frequent adverse events (occurring at ≥ 5%) reported in children upon dose initiation were insomnia, affect liability and mood swings. In the clinical trial with DYANAVEL XR Tablets, the most frequent adverse events (occurring at ≥5%) were insomnia, irritability, anxiety, decreased appetite, dry mouth, nausea, headache and tachycardia. There were no adverse events leading to discontinuation with DYANAVEL Oral Suspension. Adverse events leading to discontinuation in 3 patients treated with DYANAVEL XR Tablets included blood pressure increased, central nervous system stimulation and anxiety. There were no serious adverse events (SAEs) in any study.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect the frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

The clinical trial program for DYANAVEL XR tablets included exposures in 127 adult patients (18-60 years of age) with ADHD enrolled in a randomized, double-blind, fixed-dose, placebo-controlled study. The information included in this section is based on data from this study. Adverse reactions were assessed by collecting treatment emergent adverse events (TEAEs) including risk of suicidality using the Columbia Suicide Severity Rating Scale, vital signs (blood pressure and heart rate) elicitation of sleep disturbances, appetite, mood, and psychotic adverse events. Adverse events reported in the study with doses of 5, 10, 15 and 20 mg once daily for up to 5 weeks are presented in Table 2. The stated frequencies represent the proportion of individuals who experienced, at least once, a TEAE of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Table 2 - Treatment Emergent Adverse Events Reported by ≥ 1% of Adults Receiving Weekly Fixed Ascending Doses of DYANAVEL XR Tablet from 5 mg up to a Final Dose of 20 mg/day*

Preferred Term	Placebo N = 65 n (%)	DYANAVEL XR Tablet N = 62 n (%)
Psychiatric disorders		
Insomnia	8 (12.3)	14 (22.6)
Initial insomnia	3 (4.6)	5 (8.1)
Irritability	5 (7.7)	11 (17.7)
Anxiety	0	5 (8.1)
Dysphoria	0	3 (4.8)
Affect lability	0	2 (3.2)
Anhedonia	1 (1.5)	1 (1.6)
Bruxism	1 (1.5)	1 (1.6)

Preferred Term	Placebo N = 65 n (%)	DYANAVEL XR Tablet N = 62 n (%)
Change in sustained attention	1 (1.5)	1 (1.6)
Libido decreased	1 (1.5)	1 (1.6)
Mood altered	0	2 (3.2)
Sleep disorder	1 (1.5)	1 (1.6)
Metabolism and nutrition disorders		
Decreased appetite	14 (21.5)	30 (48.4)
Increased appetite	2 (3.1)	2 (3.2)
Gastrointestinal disorders		
Dry mouth	1 (1.5)	12 (19.4)
Nausea	2 (3.1)	5 (8.1)
Constipation	2 (3.1)	1 (1.6)
Vomiting	3 (4.6)	0
Abdominal discomfort	1 (1.5)	1 (1.6)
Nervous system disorders		
Headache	4 (6.2)	8 (12.9)
Dizziness	1 (1.5)	5 (8.1)
Migraine	2 (3.1)	0
General disorders and administration site conditions		
Fatigue	4 (6.2)	1 (1.6)
Feeling jittery	1 (1.5)	2 (3.2)
Thirst	2 (3.1)	2 (3.2)
Infections and infestations		
Bronchitis	1 (1.5)	2 (3.2)
Pharyngitis	0	2 (3.2)
Upper respiratory tract infection	0	2 (3.2)
Investigations		
Blood pressure increased	1 (1.5)	1 (1.6)
Blood pressure systolic increased	1 (1.5)	1 (1.6)
Skin subcutaneous tissue disorders		
Hyperhydrosis	0	3 (4.8)
Acne	0	2 (3.2)
Cardiac disorders		
Tachycardia	0	5 (8.1)

*Subjects randomized to DYANAVEL XR Tablets were titrated in increments of 5 mg each week to a final dose of 20 mg for 14(+/- 3) days. Subjects who could not tolerate study drug at any dose were discontinued from study. Treatment-emergent adverse events reported above reflect events occurring at any dose over the 5 weeks.

8.2.1. Clinical Trial Adverse Reactions – Pediatrics

Adverse events reported in ≥1% of patients in the phase 3, dose-optimized, randomized, double-blind, placebo-controlled laboratory-based classroom study of pediatric patients with ADHD (aged 6 to 12 years) treated with DYANAVEL XR Oral Suspension are presented in the following table. TEAEs and frequencies were recorded as outlined above. All patients were treated with DYANAVEL XR Oral Suspension for 5

weeks, with doses escalating each week (to a maximum of 20 mg/day) until the optimum dose was achieved according to patient tolerance. At Week 6, patients were randomized in a 1:1 ratio to placebo or to remain on optimized treatment.

Table 3 - Treatment-Emergent Adverse Events Reported by ≥ 1% of Children (6 to 12 years of age) in up to 5 weeks Open-Label, Dose-Titration Period followed by a 1 week Double-Blind, Placebo-Controlled Treatment Period*

Preferred Term	Open Label Dose-Optimization Period (5 weeks) N = 107 n (%)	Double-Blind Placebo-Controlled Period (1 week)	
		Placebo (N=48) n (%)	DYANAVEL XR Oral Suspension (N=52) n (%)
Psychiatric disorders			
Insomnia	14 (13.1)	1 (2.1)	1 (1.9)
Initial insomnia	0	1 (1.2)	0
Affect lability	10 (9.3)	0	0
Mood swings	6 (5.6)	0	0
Dysphoria	4 (3.7)	0	0
Irritability	4 (3.7)	0	0
Aggression	2 (1.9)	0	0
Tearfulness	2 (1.9)	0	0
Metabolism and nutrition disorders			
Decreased appetite	28 (26.2)	0	1 (1.9)
Gastrointestinal disorders			
Abdominal pain upper	8 (7.5)	1 (2.1)	2 (3.8)
Nausea	5 (4.7)	0	0
Vomiting	4 (3.7)	1 (2.1)	1 (1.9)
Apthous stomatitis	2 (1.9)	0	0
Injury, poisoning and procedural complications			
Arthropod bite	2 (1.9)	1 (2.1)	0
Muscle strain	2 (1.9)	0	0
Nervous system disorders			
Headache	6 (5.6)	1 (2.1)	1 (1.9)
Dizziness	2 (1.9)	0	0
Sudden onset of sleep	0	1 (2.1)	0
Infections and infestations			
Gastroenteritis viral	2 (1.9)	1 (2.1)	1 (1.9)
Upper respiratory tract infection	2 (1.9)	1 (2.1)	0
General disorders and administration site conditions			
Fatigue	5 (4.7)	0	0
Malaise	0	1 (2.1)	0
Pyrexia	0	1 (2.1)	0
Respiratory, thoracic and mediastinal disorders			
Cough	5 (4.7)	0	0
Epistaxis	0	0	2 (3.8)

Preferred Term	Open Label Dose-Optimization Period (5 weeks) N = 107 n (%)	Double-Blind Placebo-Controlled Period (1 week)	
		Placebo (N=48) n (%)	DYANAVEL XR Oral Suspension (N=52) n (%)
Rhinitis allergic	0	0	2 (3.8)
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain	0	0	1 (1.9)
Investigations			
Weight decreased	3 (2.8)	0	0

* Study TRI102-ADD-001 was a Phase 3 dose-optimized, randomized double-blind, placebo-controlled, parallel-group laboratory-based classroom study in pediatric patients aged 6 to 12 years. Participants were titrated up from a starting dose of 2.5 or 5.0 mg/day for 5 weeks to a stable dose of 10 to 20 mg/day and were then randomized to double-blind treatment with either the optimal dose of DYANAVEL XR Oral Suspension that was established in the open-label, dose optimization phase, or to placebo, for one week.

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.

8.5. Post-Market Adverse Reactions

- **Suicidal Behaviour and Ideation**
    - There have been post-marketing reports of suicide-related events, including completed suicide, suicide attempt, and suicidal ideation in patients treated with ADHD medications. In some of these reports, comorbid conditions may have contributed to the event (see 7 Warnings and Precautions, Suicidal Behaviour and Ideation).
- **Adverse Events Reported with Other Amphetamine Products**
    - 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)
- Endocrine: impotence, changes in libido, frequent or prolonged erections
- Eye Disorders: vision blurred, mydriasis
- Gastrointestinal: unpleasant taste, constipation, intestinal ischemia, and other gastrointestinal disturbances
- Investigations: QTc Prolongation
- Musculoskeletal, Connective Tissue, and Bone Disorders: rhabdomyolysis Psychiatric Disorders: dermatillomania, bruxism
- Skin: alopecia
- Vascular Disorders: Raynaud's phenomenon, epistaxis, contusion

9. Drug Interactions

9.1. Serious Drug Interactions

- Co-Administration of Monoamine Oxidase Inhibitors (MAOIs); see 2 Contraindications, 9.4 Drug-Drug Interactions, Monoamine Oxidase Inhibitors (MAOIs)

9.2. Drug Interactions Overview

- Because of possible increases in blood pressure and heart rate, DYANAVEL XR should be used cautiously with drugs with similar pharmacological actions.
- Alcohol should be avoided while taking DYANAVEL XR.
- Downward dose adjustment of anticoagulants, anticonvulsants and some antidepressants may be required when given concomitantly with amphetamines.
- DYANAVEL XR should not be used concomitantly with monoamine oxidase inhibitors (MAOIs) or within 14 days after discontinuing MAOI treatment.
- **Serotonergic Drugs:** On rare occasions, serotonin syndrome has occurred in association with the use of amphetamines, such as DYANAVEL XR when given in conjunction with serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) (see 7 Warnings and Precautions, Serotonin toxicity / Serotonin syndrome). It has also been reported in association with overdose of amphetamines, including DYANAVEL XR (see 5 Overdose).

  As these syndromes may result in potentially life-threatening conditions (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma), treatment with serotonergic drugs should be discontinued if such events occur and supportive symptomatic treatment should be initiated. DYANAVEL XR should be used with caution in combination with serotonergic and/or neuroleptic drugs (e.g. triptans, certain

tricyclic antidepressants and opiate analgesics, lithium, St. John's Wort, MAOI) due to the risk of serotonergic syndrome (see 7 Warnings and Precautions, Serotonin toxicity / Serotonin syndrome).

9.3. Drug-Behaviour Interactions

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. Patients should be advised not to consume alcohol while taking DYANAVEL XR. Consumption of alcohol while taking DYANAVEL XR may result in a more rapid release of the dose of amphetamine

9.4. Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 – Established or Potential Drug-Drug Interactions

Therapeutic class	Source of Evidence	Effect	Clinical comment
Gastrointestinal acidifying agents (e.g. guanethidine, reserpine, glutamic acid HCl, ascorbic acid, etc.)	T	Gastrointestinal acidifying agents may lower blood levels and efficacy of DYANAVEL XR (amphetamine).	Increased dose of DYANAVEL XR may need to be considered when taken concomitantly with acidifying agents based on patient's response.
Acidifying Agents (Urinary and gastrointestinal) (e.g. ammonium chloride, sodium acid phosphate, etc.)	T	Lower blood levels and efficacy of amphetamine. Urinary acidifying agents increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion.	Increased dose of DYANAVEL XR may need to be considered when taken concomitantly with acidifying agents based on patient's response.
Adrenergic blockers	T	Adrenergic blockers are inhibited by amphetamines.	Caution should be taken with concomitant administration with DYANAVEL XR.
Gastrointestinal and urinary alkalinizing agents (e.g. sodium bicarbonate, antacids, acetazolamide, some thiazides)	T	Gastrointestinal and urinary alkalinizing agents Increase blood level and potentiate the action of amphetamine.	Co-administration of DYANAVEL XR and gastrointestinal or alkalinizing agents should be avoided.

Therapeutic class	Source of Evidence	Effect	Clinical comment
Proton Pump Inhibitors	T	Proton Pump inhibitors act on proton pumps by blocking acid production thereby reducing gastric acidity.	Co-administration with DYANAVEL XR and proton pump inhibitors should be avoided.
Antidepressants, tricyclic (e.g. desipramine, protriptyline)	T	Amphetamines may enhance the activity of tricyclic antidepressant or sympathomimetic agents *d*-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of *d*-amphetamine in the brain. Cardiovascular effects can be potentiated.	Monitor frequently and adjust dosage or use alternative therapy based on patient's response.
Monoamine oxidase inhibitor antidepressants, furazolidone metabolite	T	MAO inhibitors slow amphetamine metabolism, potentiating their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings. May cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results.	Do not administer DYANAVEL XR concomitantly with monoamine oxidase inhibitors (MAOIs) or within 14 days after discontinuing MAOI treatment.
Antihistamines	T	Amphetamines may counteract the sedative effect of some antihistamines.	Caution should be taken with concomitant administration with DYANAVEL XR Oral Suspension or DYANAVEL XR.
Antihypertensives	T	Amphetamines may antagonize the hypotensive effects of antihypertensives.	Caution should be taken with concomitant administration with DYANAVEL XR. It is recommended to monitor blood pressure and adjust the dosage of the antihypertensive drug as needed (see 7 Warnings and Precautions, Hypertension and Other Cardiovascular Conditions).

Therapeutic class	Source of Evidence	Effect	Clinical comment
Chlorpromazine	T	Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.	Caution should be taken with concomitant administration with DYANAVEL XR
Serotonergic drugs (e.g., SSRIs, SNRIs, triptans)	T	The concomitant use of DYANAVEL XR with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort increase the risk of Serotonin syndrome.	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).
Ethosuximide	T	Amphetamines may delay intestinal absorption of ethosuximide.	Caution should be taken with concomitant administration with DYANAVEL XR
Haloperidol	T	Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.	Caution should be taken with concomitant administration with DYANAVEL XR.
Lithium carbonate	T	The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.	Caution should be taken with concomitant administration with DYANAVEL XR.
Meperidine	T	Amphetamines potentiate the analgesic effect of meperidine.	Caution should be taken with concomitant administration with DYANAVEL XR.
Methenamine therapy	T	Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.	Caution should be taken with concomitant administration with DYANAVEL XR.
Norepinephrine	T	Amphetamines enhance the adrenergic effect of norepinephrine.	Caution should be taken with concomitant administration with DYANAVEL XR.

Therapeutic class	Source of Evidence	Effect	Clinical comment
Phenobarbital	T	Amphetamines may delay intestinal absorption of phenobarbital; co- administration of phenobarbital may produce a synergistic anticonvulsant action.	Caution should be taken with concomitant administration with DYANAVEL XR.
Phenytoin	T	Amphetamines may delay intestinal absorption of phenytoin; co- administration of phenytoin may produce a synergistic anticonvulsant action.	Caution should be taken with concomitant administration with DYANAVEL XR.
Propoxyphene	T	In cases of propoxyphene overdose, amphetamine CNS stimulation is potentiated, and fatal convulsions can occur.	Caution should be taken with concomitant administration with DYANAVEL XR.
Veratrum alkaloids	T	Amphetamines inhibit the hypotensive effect of veratrum alkaloids.	Caution should be taken with concomitant administration with DYANAVEL XR.

C = Case Study; CT = Clinical Trial; T = Theoretical

9.5. Drug-Food Interactions

Food does not affect the extent of absorption of DYANAVEL XR. No significant differences were found between fed and fasted conditions (see 4.2 Recommended Dose and Dosage Adjustment, 10.3 Pharmacokinetics).

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's Wort can increase serotonin levels in the brain and can therefore contribute to the risk of serotonin toxicity if DYANAVEL XR is prescribed with other serotonergic drugs.

9.7. 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.

10. Clinical Pharmacology

10.1. 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.

10.2. Pharmacodynamics

The behavioral manifestations of ADHD are believed to involve an interactive imbalance between dopaminergic and other neurotransmitter systems. Amphetamine increases the availability of synaptic dopamine at key sites in the brain by stimulating its release from newly synthesized (cytoplasmic) dopamine pools.

DYANAVEL XR has a tablet and oral suspension formulation that uses a drug delivery technology called LiquiXR® made up of resin bound uncoated immediate release drug and extended-release drug with variable coating. The combination of free drug, resin-bound uncoated drug and resin bound coated drug with variable thickness coating results in continuous release of amphetamine.

In addition to a dopaminergic mechanism of action, there is experimental evidence to suggest involvement of other neurotransmitter systems in the regulation of behavioral effects (e.g., motor activity). These include interactions between dopaminergic, GABAergic and glutamatergic pathways and possible involvement of cholinergic pathways.

Amphetamine-induced effects are primarily mediated by D1 and D2 receptors. In addition, 5-HT2A and 5-HT3 receptors, and NMDA receptors are suggested to play a role in amphetamine-induced release of dopamine and in the regulation of the firing rate and pattern of midbrain dopamine neurons, respectively.

Prenatal exposure to amphetamine was associated with a variety of responses in offspring that included increases in conditioned avoidance, exploratory behavior and sexual behavior and decreases in 5-HT content in the medial hypothalamus.

Repeated administration of high concentrations of amphetamine produced striatal, neostriatum and frontal cortex dopamine nerve fiber degeneration.

Amphetamine interacted with a variety of compounds that included caffeine, cocaine, morphine, diazepam, phencyclidine, clonidine, fluoxetine, lithium, pentobarbital, ethanol and THC. The mechanism of many of these interactions is currently not known.

10.3. Pharmacokinetics

Pharmacokinetic Results in Healthy Adults

Table 5 – Summary of d- and l-Amphetamine Pharmacokinetic Parameters in Healthy Adults under Fasted Conditions[1]

	d-Amphetamine				l-Amphetamine			
Dose of amphetamine base	**C_{max}**	**median T_{max} (h)**	**$t_{½}$ (h)**	**$AUC_{0-\infty}$**	**C_{max}**	**median T_{max} (h)**	**$t_{½}$ (h)**	**$AUC_{0-\infty}$**
20 mg (chewed ER Tablet)	54.71	5.0	13.9	1206.43	17.47	5.0	17.8	472.66

	d-Amphetamine				l-Amphetamine			
Dose of amphetamine base	**C_{max}**	**median T_{max} (h)**	**$t_{½}$ (h)**	**$AUC_{0-\infty}$**	**C_{max}**	**median T_{max} (h)**	**$t_{½}$ (h)**	**$AUC_{0-\infty}$**
20 mg (ER oral suspension)	54.13	4.0	12.4	1197.32	17.29	4.0	15.1	461.54

[1]Values reported are arithmetic means unless indicated otherwise.
ER=extended release

No differences were found between fed and fasted conditions.

Pharmacokinetic Results in Pediatric Patients

Table 6 - Summary of d- and l-Amphetamine Pharmacokinetic Parameters in Pediatric Patients (6-12 years old) under Fasting Conditions[1]

	d-Amphetamine				l-Amphetamine			
Dose of amphetamine base	**C_{max}**	**median T_{max} (h)**	**$t_{½}$ (h)**	**$AUC_{0-\infty}$**	**C_{max}**	**median T_{max} (h)**	**$t_{½}$ (h)**	**$AUC_{0-\infty}$**
10 mg (ER oral suspension, fasting conditions)	54.87	3.4	10.6	1061.20	17.15	5.0	12.5	380.53

[1]Values reported are arithmetic means unless indicated otherwise.
ER=extended release

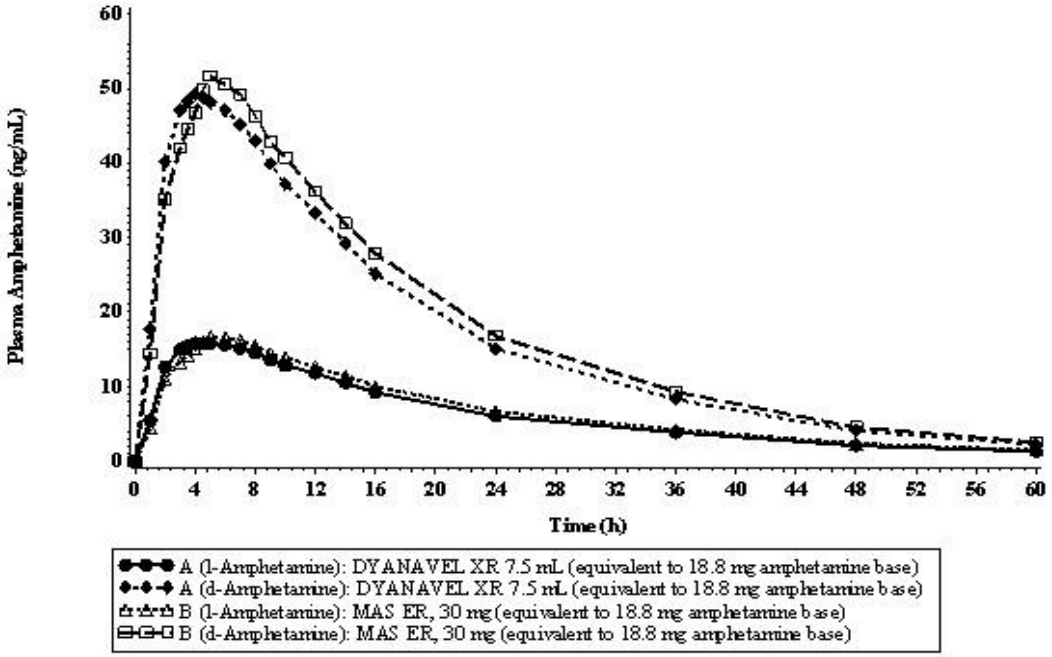
Absorption

Extended-Release Oral Suspension

Following a single 18.75 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.

Following a single 18.75 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) mixed amphetamine salts (MAS) capsules. The relative bioavailability of DYANAVEL XR compared with an equal dose of ER mixed amphetamine salts (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 in Adults

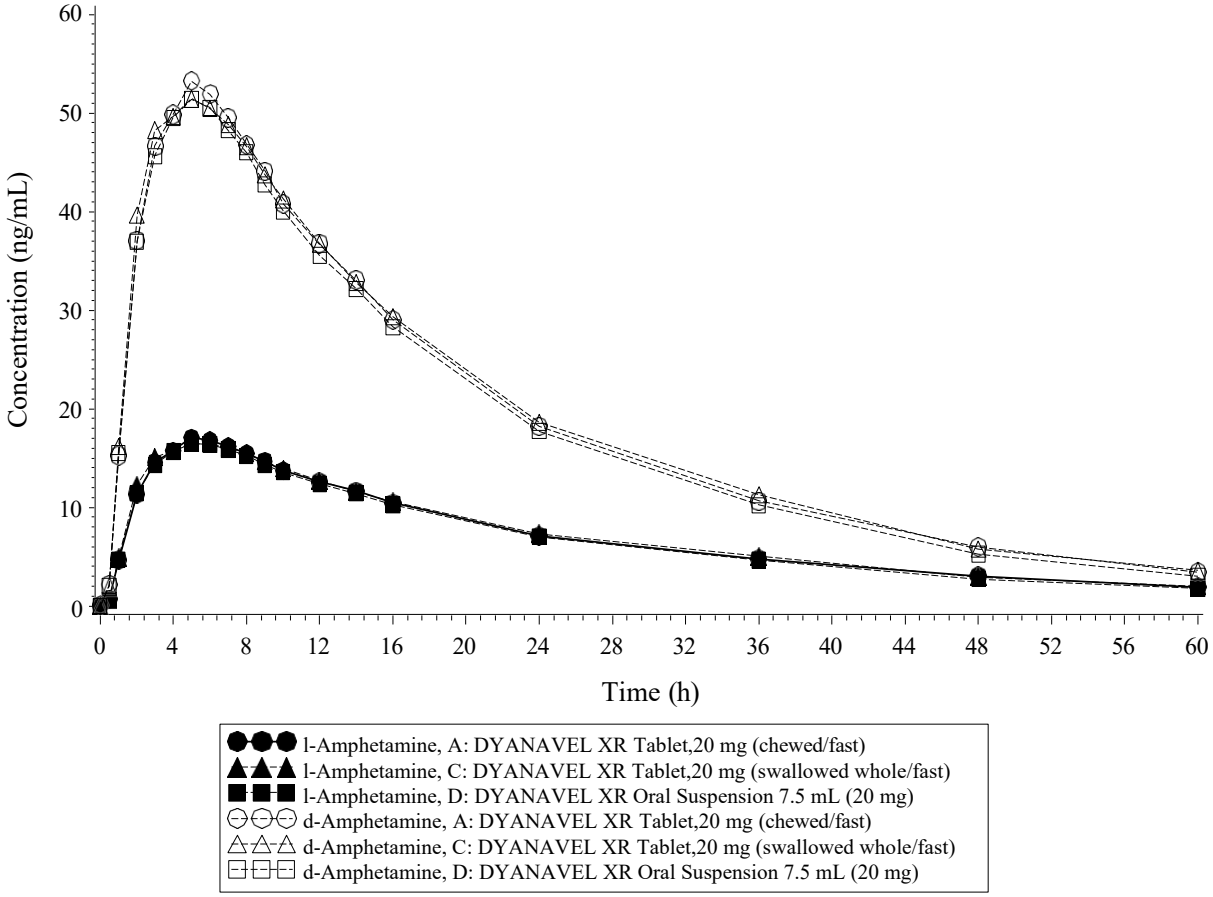


Extended-Release Tablet

Following a single 20 mg dose of DYANAVEL XR extended-release tablets (swallowed whole) to 32 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 in Healthy Adults



Effect of Food

Extended-Release Oral Suspension

Ingestion of 7.5 mL 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.

Distribution

Literature studies indicated a stereospecific distribution of the individual dextro (d-) and levo (l-) enantiomers of amphetamine in the brain and heart of mice. Distribution kinetics in the rat indicated that similar amounts of both enantiomers were excreted in the urine as parent drug and as the hydroxy metabolite.

Radiolabelled ^{3}H-*d*-amphetamine was distributed in many tissues of pregnant and non-pregnant female

and male mice. Amphetamine crossed the placenta and was present in the placenta, whole fetus, and in fetal brain and liver. Fetal tissue concentrations were generally much lower than maternal tissue concentrations.

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.

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 7.5 mL (2.5 mg/mL) 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.

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.

Special Populations and Conditions

- **Pediatrics:** Following a single 10 mg dose of DYANAVEL XR extended-release oral suspension (2.5 mg/mL) 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 3.4 and 5 hours after dosing, respectively. The mean plasma terminal elimination half-lives of d- and l-amphetamine were 10.6 hours and 12.5 hours, respectively.
- **Geriatrics:** Specific studies of DYANAVEL XR in geriatric patients have not been conducted.
- **Sex:** There is insufficient experience with the use of DYANAVEL XR to detect gender variations in pharmacokinetics.
- **Ethnic Origin:** There is insufficient experience with the use of DYANAVEL XR to detect ethnic variations in pharmacokinetics.
- **Pregnancy and Breast-feeding:** 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 dose 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, breastfeeding is not recommended during treatment with DYANAVEL XR.

- **Hepatic Insufficiency:** There is no experience with the use of DYANAVEL XR in patients with hepatic insufficiency. However, a fraction of amphetamine dose has been reported to undergo hepatic metabolism; consequently hepatic impairment has the potential to inhibit the elimination of amphetamine and result in prolonged exposures.
- **Renal Insufficiency:** No specific studies have been conducted to evaluate the effect of renal 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, as amphetamine is not dialyzable. Consequently, renal dysfunction has the potential to inhibit the elimination of amphetamine and result in prolonged exposures.

11. Storage, Stability, and Disposal

Store DYANAVEL XR at 15°C to 30°C.

DYANAVEL XR extended-release oral suspension: Dispense in a tight container with child resistant closure. Once the oral suspension bottle is opened, the marketed pack should be discarded appropriately within 6 months from the date of opening (or upon the expiry date, whichever is first). The pharmacy container should be discarded appropriately within 40 days after dispensing.

Dispose of remaining, unused, or expired DYANAVEL XR Oral Suspension or DYANAVEL XR Tablets at the pharmacy. Do not discard with household trash.

DYANAVEL XR should be kept in a safe place, such as under lock and out of the sight and reach of children before, during and after use to prevent inappropriate or accidental use by others.

Unused or expired DYANAVEL XR should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. DYANAVEL XR should not be shared with others and steps should be taken to protect it from theft or misuse. The patient should speak to their pharmacist about temporary storage options, if required, until the medication can be returned to the pharmacy for safe disposal.

Part 2: Scientific Information

13. Pharmaceutical Information

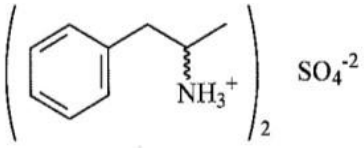
Drug Substance

Proper name: Amphetamine Sulfate

Chemical name: Phenyl-2-(R,S)-aminopropane sulfate

Molecular formula and molecular mass: $C_{18}H_{28}N_2SO_4$, 368.5 g/mol

Structural formula:



Physicochemical properties: White to off-white crystalline powder

pH: 5.0 to 6.0, of the aqueous solution

pKa: 9.9

Solubility: Soluble in water and slightly soluble in alcohol

Melting Point: 131 to 135°C (of n-benzoyl derivative of amphetamine)

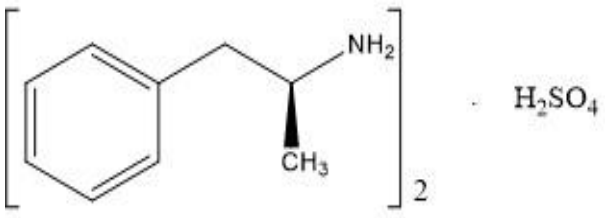
Proper name: Dextroamphetamine Sulfate

Chemical name:

1) Phenyl-2-(S)-aminopropane sulfate
2) (+)-α-Methylphenethylamine sulfate (2:1)
3) Benzeneethanamine, α-methyl-, (S)-, sulfate (2:1)

Molecular formula and molecular mass: $C_{18}H_{28}N_2SO_4$, 368.49 g/mol

Structural formula:



Physicochemical properties: White crystalline powder

pH: 5.0 to 6.0, of aqueous solution

pKa: 9.9

Solubility: Soluble in water and slightly soluble in alcohol

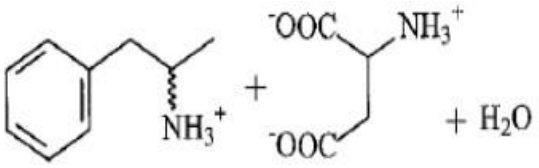
Melting Point: 155 to 160°C (of n-benzoyl derivative of amphetamine)

Proper name: Amphetamine Aspartate Monohydrate

Chemical name: Phenyl-2-(R,S)-aminopropane aspartate

Molecular formula and molecular mass: $C_{13}H_{22}N_2O_5$, 286.3 g/mol

Structural formula:



Physicochemical properties: White to off-white crystalline powder

pH: 5.0 to 7.0 of the aqueous solution

pKa: 9.9

Solubility: Soluble in water and slightly soluble in alcohol

Melting Point: 131 to 135°C (of n-benzoyl derivative of amphetamine)

14. Clinical Trials

14.1. Clinical Trials by Indication

Attention-Deficit Hyperactivity Disorder (ADHD)

DYANAVEL XR Oral Suspension

Table 7 - Summary of patient demographics for the pivotal clinical trial of DYANAVEL XR Oral Suspension in pediatric patients aged 6-12 years with ADHD[1]

Study #	Study Design	Dosage, route of administration, and duration	Study subjects (n)	Mean age (Range)	Sex
TRI102-ADD-001	Phase 3, dose-optimized, randomized, double- blind, placebo-controlled, multicenter, parallel-group, laboratory classroom study	Open label dose optimization period (5-weeks): 2.5 to 20 mg/day oral doses Double-blind period (1 week): oral dose determined during open-label phase, once per day	Total: (99) Placebo: (48) DYANAVEL XR oral suspension: (51)	9.2 years (6-12 years)	68 M 31 F

[1] Intent to treat (ITT) population

The efficacy of DYANAVEL XR oral suspension was evaluated in a Phase 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter laboratory classroom study conducted in 107 pediatric patients (aged 6 to 12 years) with ADHD (according to DSM-IV criteria). 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 (dose based on investigator's discretion). 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 period with the individually optimized dose of DYANAVEL XR or placebo. There was a practice laboratory classroom session before the randomized, controlled phase. 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 endpoint was the assessment of change from pre-dose in model-adjusted SKAMP-Combined scores at 4 hours post-dose measured during the laboratory school day (Visit 8) in the ITT Population. The primary efficacy analysis at 4 hours post-dose, showed a statistically significant difference in the DYANAVEL XR Oral Solution group relative to the placebo group (treatment difference LS mean [SE]: -14.8 [1.61], p <0.001).

Table 8 - Summary of Primary Efficacy Results in Pediatric Patients (6-12 years) with ADHD[1]

	Study TRI102-ADD-001		
	DYANAVEL XR Extended Release Oral Suspension n = 51	**Placebo n = 48**	**Treatment difference (95% CI)**
Primary endpoints			
SKAMP Combined Score			
Mean Pre-dose Score (SD)	17.3 (8.9)	15.5 (7.4)	---
LS Mean Change from Pre-dose at 4 hours Post-Dosing (SE)	-8.8 (1.14)	6.0 (1.2)	-14.8 (-17.9, -11.6)[2] p < 0.0001

SD = Standard deviation; SE = Standard error; LS Mean = Least squares mean; CI = confidence interval
SKAMP: Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale

The SKAMP-Combined score is obtained by summing items 1-13, where each item is rated on a 7-point scale (0=normal to 6=maximal impairment).

Treatment comparisons for change from pre-dose scores are assessed using a mixed model repeated measures analysis, with treatment (TRI102/placebo), study center, time point, and time point-by-treatment interaction as main effects, and subject intercept as a random effect.

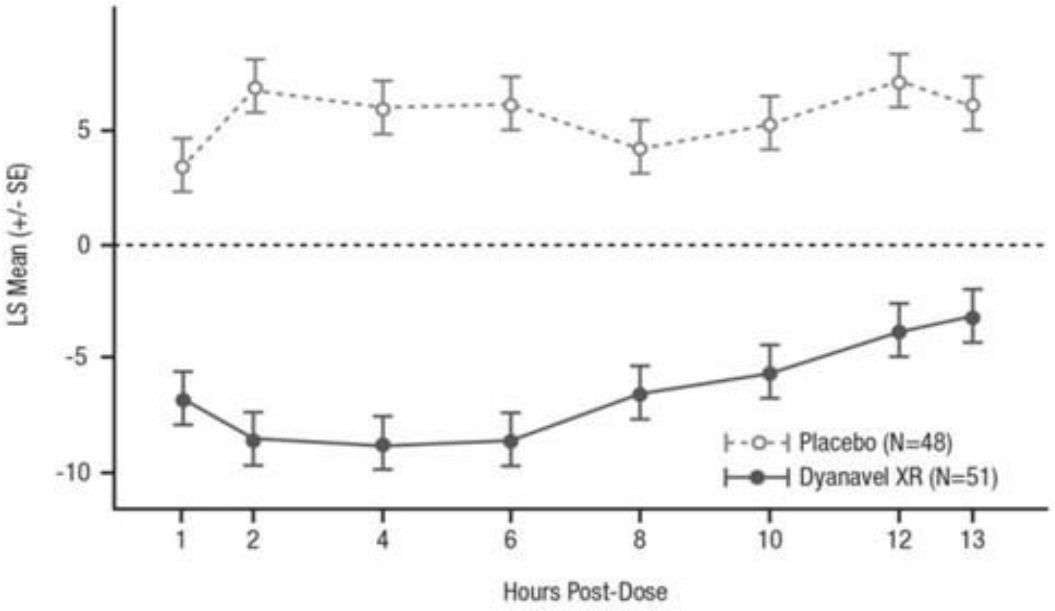
[1] Intent to treat (ITT) population
[2] Difference (drug minus placebo) in least squares mean change from pre-dose

Key secondary endpoints included onset of clinical effect, defined as the earliest post-dose time point at which the SKAMP-Combined score difference between the 2 treatments is statistically significant (p<0.05) and duration of clinical effect, defined as the difference between the onset time and the latest consecutive time point at which the SKAMP-Combined score difference between the 2 treatments is still

statistically significant ($p<0.05$).

Results from the double-blind, placebo-controlled week of the study are summarized in Table 8 and Figure 3.

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



The onset of treatment effect was observed at the earliest time point assessed, 1 hour post-dose. The duration of efficacy persisted until the final time point at 13 hours post-dose. The highest magnitude of effect relative to pre-dose in the DYANAVEL XR group occurred at the 4-hour post-dose time point and the highest treatment difference relative to placebo occurred at 2 hours post-dose.

DYANAVEL XR Tablets

Table 9 - Summary of patient demographics for the pivotal clinical trial of DYANAVEL XR Tablets in adults aged 18-60 years with ADHD (TRI-108-ADD-400)[1]

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
TRI-108-ADD-400	Phase 3, randomized, double-blind, placebo-controlled, parallel-group study	5 week double-blind titration (placebo or DYANAVEL XR Tablet; starting dose 5 mg orally, titrated up by 5 mg increments each week) Final dose of 20 mg for 14 days.	Total: (127) Placebo: (65) DYANAVEL XR Tablet: (62)	32.4 years (18-60 years)	76 M 51 F

[1] Intent to treat (ITT) population

Study TRI-108-ADD-400 was a randomized, double-blind (DB), placebo-controlled, parallel study to assess the efficacy and safety of DYANAVEL XR Tablets compared with placebo for the treatment of ADHD in adults aged 18 to 60 years. After screening and baseline evaluations were completed, eligible subjects were randomized to DYANAVEL XR Tablets or matching placebo taken orally once daily in the morning beginning the day after the Baseline visit.

Following randomization, subjects underwent a 5-week double-blind dose-titration phase. Subjects were administered a starting dose of 5 mg DYANAVEL XR Tablets or matching placebo, with or without food, swallowed whole or chewed, in the morning before 10 am. Subjects were then titrated up by 5 mg increments each week. After Visit 3, subjects received a final dose of 20 mg for 14 (±3) days before Visit 5. Subjects who could not tolerate the study drug were discontinued from the study.

A Permanent Product Measure of Performance (PERMP) placement test was administered at screening or baseline. PERMP practice sessions were done before and after efficacy and safety assessments during baseline and Visits 1 to 3. An abbreviated administration of serial PERMP tests took place at Visit 4 where the PERMP was administered pre-dose, and at 0.5, 1, 2 and 4 hours post-dose. At Visit 5, efficacy assessments included the administration of serial PERMPs pre-dose and at 0.5, 1, 2, 4, 8, 10, 12, 13, and 14 hours post-dose.

Table 10 – Summary of Primary Efficacy Results in Adult Patients with ADHD[1]

	Study TRI108-ADD-400		
	DYANAVEL XR Tablets N = 45	**Placebo N = 46**	**Treatment difference[2] [95% CI]**
Primary endpoint PERMP-T scores at Visit 5			
Predose mean (SD)	259.5 (69.4)	260.6 (77.8)	
Over all postdose timepoints			
Mean (SD)	302.8 (87.6)	279.6 (79.8)	
Adjusted mean (SE)[2]	303.4 (5.9)	279.0 (5.8)	24.3 (8.3) [7.8, 40.8] p = 0.0043[3]
95% CI for adjusted mean[2]	(291.6, 315.1)	(267.4, 290.6)	

PERMP-T = Permanent Product Measure of Performance Total. PERMP-T score ranges from 0 to 800 with higher scores indicating better performance. SD = standard deviation, SE = standard error

N = number of subjects.

[1]Modified Intent-to-Treat Population (mITT) is comprised of subjects who completed the study.

[2]Adjusted mean (SE), treatment difference between adjusted mean (DYANAVEL XR Tablets – Placebo), 95% CI of difference and p-value are based on mixed model repeated measures (MMRM) analysis model with treatment, time, and treatment-by-time as fixed effects, and subject as a random effect. Predose PERMP-T scores are included as covariate.

[3]Two-sided p-value

The primary efficacy endpoint, mean post-dose PERMP-T score, over all post-dose time points at Visit 5 was statistically significantly higher in the DYANAVEL XR tablets group (302.8) compared to the placebo group (279.6) (p-value = 0.0043).

16. Non-Clinical Toxicology

General toxicology: Administration of amphetamine (d- or d, l-) have been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage in adult rodents. The significance of these findings to humans is unknown.

Genotoxicity: Amphetamine, in the enantiomer 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.

Carcinogenicity: 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.

Reproductive and developmental toxicology: Amphetamine, in the enantiomer ratio (d- to l- 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).

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 of up to 6 and 16 mg/kg/day, respectively. These doses 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, a number of studies in rodents indicate that prenatal or early postnatal administration of amphetamine (d- or d,l-), at doses which provide similar exposure 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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

DYANAVEL® XR

Amphetamine Extended-Release Oral Suspension

This Patient Medication Information is written for the person who will be taking **DYANAVEL XR**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **DYANAVEL XR**, talk to a healthcare professional.

Serious warnings and precautions box

- **Like other stimulants, the use of DYANAVEL XR may lead to abuse, misuse or dependence. This means you may feel like you need to take more of it over time, or that it would be difficult for you to stop taking it. If you think this is happening to you, talk to your healthcare professional.**
- **Misusing DYANAVEL XR may cause serious heart problems and even sudden death.**

What DYANAVEL XR is used for:

- Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 to 12 years of age and adults (18 years of age and older).

How DYANAVEL XR works:

DYANAVEL XR is an amphetamine that belongs to a group of medicines called central nervous system stimulants. It works by changing the levels of certain chemicals in the brain. This helps to increase attention and decrease impulsivity and hyperactivity in patients with ADHD.

The ingredients in DYANAVEL XR are:

Medicinal ingredients: Amphetamine (as amphetamine (complexed with sodium polystyrene sulfonate), dextroamphetamine sulfate and amphetamine aspartate).

Non-medicinal ingredients: Anhydrous citric acid, beta damascone, citral, d-limonene, ethyl acetate, ethyl butyrate, glycerin, isoamyl acetate, iso-amyl butyrate, iso-butyl acetate, methylparaben, modified starch, orange oil, polysorbate 80, polyvinyl acetate, povidone, propylene glycol, propylparaben, sodium lauryl sulfate, sodium polystyrene sulfonate, sucralose, tangerine oil, triacetin, vanillin and xanthan gum.

DYANAVEL XR comes in the following dosage forms:

Oral suspension: 2.5 mg/mL

Do not use DYANAVEL XR if you:

- Are allergic to amphetamine, or any of the ingredients in DYANAVEL XR
- Are sensitive, or allergic to any other stimulant medications (such as cold or allergy medications, or other medications used to treat ADHD)

- Are taking or have taken within the past 14 days a type of anti-depression medicine called a monoamine oxidase inhibitor (MAOI)
- Have symptoms of heart disease
- Have moderate to severe high blood pressure
- Have a condition that hardens the arteries
- Have hyperthyroidism (a condition that causes the thyroid gland to make too much of a hormone), or a condition called thyrotoxicosis
- Have glaucoma, an eye disease
- Have any condition that causes anxious and distressful feelings
- Have ever had any problems with drug or alcohol use (e.g., drinking too much, feeling like you cannot quit etc.)
- Have a condition called pheochromocytoma (a rare tumour that usually grows in the adrenal glands, above your kidneys)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DYANAVEL XR. Talk about any health conditions or problems you may have, including if you:

- Have structural heart abnormalities, symptoms of heart disease, a heart defect, serious heart rhythm problems, or other serious heart problems
- Have a family history of sudden cardiac death, or death related to heart problems.
- Have mild high blood pressure
- Have mental health problems or a family history of mental health problems, including anxiety, psychosis, mania, bipolar illness, depression, aggression or suicide
- Have a disorder that affects the blood vessels outside your heart and brain. This includes a condition called “Raynaud’s phenomenon” (a condition that causes fingers and toes to feel numb, tingle and change colour when cold)
- Have a history of seizures (convulsions or epilepsy) or abnormal EEGs (measure of brainwave activity)
- Are involved in any physical exercises that are tiring on the body
- Consume alcohol
- Have or have a family history of motion tics, verbal tics, or Tourette’s syndrome
- Take other drugs for the treatment of ADHD
- Have kidney problems or are on dialysis
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed. DYANAVEL XR passes into your breast milk. You and your healthcare professional should decide if you will take DYANAVEL XR or breastfeed

Other warnings you should know about:

Serotonin toxicity (also known as Serotonin Syndrome): DYANAVEL XR may cause serotonin syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles

and digestive system work. You may develop serotonin toxicity if you take DYANAVEL XR with other serotonergic drugs such as antidepressant or migraine medications.

Serotonin toxicity symptoms include:

- Fever, sweating, shivering, diarrhea, nausea, vomiting
- Muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination
- Fast heartbeat, changes in blood pressure
- Confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, coma

Heart related problems: The following heart related problems have been reported in people taking medicine like DYANAVEL XR, to treat ADHD:

- Sudden death in patients who have heart problems or heart defects
- Stroke and heart attack
- Increased blood pressure and heart rate

Sudden death has been reported in children and adolescents treated with drugs for ADHD. Those children and adolescents had problems with the structure of their heart or had other serious heart problems. DYANAVEL XR generally should not be used in patients who have any serious heart diseases or conditions, such as

- high blood pressure
- problems with the structure of their heart
- diseases that impact the muscles of their heart
- serious problems with their heartbeat

Seek immediate medical help if you have any signs of heart problems such as chest pain, shortness of breath, or fainting while taking DYANAVEL XR.

Mental health problems: The following mental health problems have been reported in people taking medicines like DYANAVEL XR, to treat ADHD:

- New or worse thoughts or feelings related to suicide (thinking about or feeling like killing yourself) and suicide attempt
- New or worse bipolar disorder (extreme mood swings, alternating from feelings of unusual excitement, over-active or un-inhibited, to feelings of depression, sadness, worthlessness or hopelessness)
- New or worsening aggressive behavior, anxiety, agitation or hostility
- New symptoms of psychosis (such as hearing voices, believing things that are not true, being suspicious)

These mental health problems are more likely to happen if you have known or unknown mental health conditions. These symptoms can happen at any time during treatment but are more likely to occur when you first start taking DYANAVEL XR, when the dose changes, or after stopping treatment.

If you experience any new or worsening mental health symptoms while taking DYANAVEL XR, talk to your healthcare professional right away.

Dependence and tolerance: Like other stimulants, DYANAVEL XR has the potential to be abused if not taken correctly. This can lead you to becoming dependent on DYANAVEL XR or feeling like you need to take more of it over time (tolerance). If you have a history of problems with drug or alcohol use (substance use disorder), discuss this with your healthcare professional.

Stopping your treatment: Do NOT change your dose or stop taking DYANAVEL XR without discussing it with your healthcare professional first. Stopping your treatment abruptly may lead to serious side effects like depression, fatigue, stomach cramps, irritability and sleeping problems. If you need to stop taking DYANAVEL XR, careful supervision by a healthcare professional is needed. To avoid side effects, your healthcare professional will work with you to slowly taper you off DYANAVEL XR.

Growth and weight loss in children: Stimulants are believed to temporarily slow growth in children. They may also lead to a higher risk of weight loss in younger children. Your child's healthcare professional will be monitoring your child's height and weight while they are taking DYANAVEL XR. If your child is not growing or gaining weight as your healthcare professional expects, your healthcare professional may stop DYANAVEL XR treatment.

Raynaud's Phenomenon: Stimulants used to treat ADHD, such as DYANAVEL XR, are associated with Raynaud's Phenomenon. During treatment with DYANAVEL XR, your healthcare professional may check for problems with your circulation in your fingers and toes, including numbness, feeling cold or pain.

Testing and check-ups: your healthcare professional may do tests before you start, and during your treatment with DYANAVEL XR. These tests may include:

- Tests that check for problems in the heart or brain
- Tests that check blood pressure and heart rate
- Blood tests to check complete blood count, platelet counts and liver enzymes

Driving or doing tasks that require special attention: DYANAVEL XR can affect your ability to perform certain tasks such as driving or using tools or machinery. Avoid doing tasks that require special attention until you know how you respond to DYANAVEL XR.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions:

Do NOT take DYANAVEL XR if you:

- are taking, or have recently taken (in the last 14 days), a type of anti-depression medicine called a monoamine oxidase inhibitor (MAOI). If you are unsure, ask your healthcare professional.

The following may also interact with DYANAVEL XR:

- other central nervous system stimulants
- alcohol
- medicines used to treat depression including St. John's Wort, selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs)

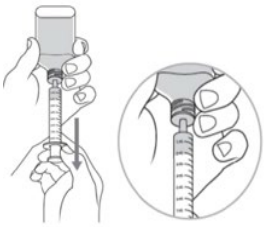
- medicines used to treat migraines, called triptans
- medicines that make urine or digestive contents more acidic (e.g., guanethidine, reserpine, ascorbic acid, ammonium chloride, sodium acid phosphate)
- medicines that make urine or digestive contents more alkaline (e.g., acetazolamide, thiazides, sodium bicarbonate, antacids)
- medicines used to reduce or increase blood pressure
- medicines used to prevent blood clots (commonly called “blood thinners”)
- cold and allergy medicines
- antipsychotic medicines (e.g., chlorpromazine, haloperidol)
- lithium
- methenamine therapy
- opioid pain medicines (e.g., meperidine, propoxyphene)
- seizure medicines (e.g., ethosuximide, phenobarbital, phenytoin)
- medicines used to block the action of epinephrine and norepinephrine
- products known as veratrum alkaloids
- medicines known as ‘proton pump inhibitors’, these reduce the amount of acid in your stomach (e.g. omeprazole)

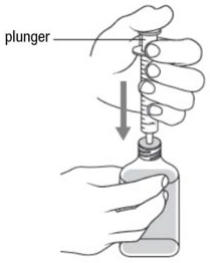
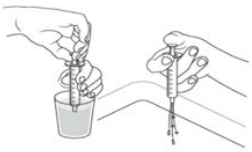
While on DYANAVEL XR, do not start taking a new medicine or herbal remedy before checking with your healthcare professional.

How to take DYANAVEL XR:

- Take DYANAVEL XR exactly as prescribed. Your healthcare professional may adjust the dose, if needed, until it is right for you. During dose adjustment, you may still have ADHD symptoms.
- Before taking DYANAVEL XR, make sure to read and follow the directions in the Instructions for Use.
- Take DYANAVEL XR one time each day in the morning. DYANAVEL XR is an extended-release medicine, meaning the medicine releases into your body throughout the day.
- DYANAVEL XR can be taken with or without food.
- Use the oral dispenser provided by your pharmacist.
- From time to time, your healthcare professional may stop DYANAVEL XR treatment for a while to check ADHD symptoms.

Instructions for Use:

<table>
<tr>
<td>Step 1:
• Check the DYANAVEL XR bottle to make sure that the bottle adaptor has been inserted into the bottle by the pharmacist. Do not remove the bottle adaptor.
• 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 adaptor is missing from the neck of the bottle.</td>
<td> 
</td>
<td>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.</td>
<td>  </td>
</tr>
<tr>
<td>Step 2:
• Shake the bottle well (up and down).</td>
<td>  </td>
<td>Step 7:
• Turn the bottle over and place upright on a counter top, then remove the oral dosing dispenser from the bottle adaptor.</td>
<td>  </td>
</tr>
<tr>
<td>Step 3:
• Check the DYANAVEL XR oral dosing dispenser to find the right dose in milliliters (mL) that you or your child’s healthcare professional has prescribed.</td>
<td> 
</td>
<td>Step 8:
• Place the tip of the oral dosing dispenser into your mouth 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.</td>
<td>  </td>
</tr>
<tr>
<td>Step 4:
• Place the DYANAVEL XR bottle upright and insert tip of the oral dosing dispenser into the bottle.</td>
<td></td>
<td>Step 9:
• Put the DYANAVEL XR cap back on the bottle and close tightly.</td>
<td>  </td>
</tr>
</table>

Step 5: • Push the plunger all the way down.		**Step 10:** • Clean the oral dosing dispenser after each use by placing in the dishwasher, or by rinsing with tap water.	

Usual dose:

Your healthcare professional will determine the best dose to treat your symptoms.

Overdose:

If you think you, or a person you are caring for, have taken too much DYANAVEL XR, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If a dose of DYANAVEL XR is missed, wait until the next day and take the usual dose at the usual time in the morning. Do not take an afternoon dose. Do not double the dose to make up for the missed dose.

Possible side effects from using DYANAVEL XR:

These are not all the possible side effects you may have when taking DYANAVEL XR. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Behavioural changes (anxiety, irritability, mood swings, nervousness)
- Chills
- Decrease or loss of appetite
- Difficulty falling asleep
- Digestive problems (constipation, diarrhea, indigestion, nausea, vomiting)
- Dizziness
- Drowsiness
- Dry mouth and thirst
- Fever
- Grinding of teeth
- Headache

- Neck pain
- Reduced sexual drive
- Sensitivity to light
- Stomachache
- Sweating
- Unpleasant taste
- Weight loss

Serious side effects and what to do about them

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Common			
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Cardiomyopathy (signs of heart muscle disease): breathlessness or swelling of the legs		✓	
Depression: feeling sad, loss of interest in usual activities, hopelessness, insomnia or sleeping too much		✓	
Dyspnea: Shortness of breath			✓
Fungal Infection		✓	
Heart palpitations or fast heart beat: skipping beats, beating too fast, pounding, fluttering rapidly		✓	
New Tics: hard to control motion tics (repeat twitching of any parts of the body) or verbal tics (repeating of sounds or words)		✓	
Urinary Tract Infection (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		✓	
Uncommon			
Aggressive Behavior, Anger or Hostility		✓	
High Blood Pressure: headaches, dizziness, lightheadedness, ringing in the ears, fainting		✓	
Trouble with vision: eyesight changes or blurred vision		✓	

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Unknown			
Condition Resembling Raynaud's Phenomenon: discoloration of the hands and feet, pain, sensations of cold and/ or numbness		✓	
Epistaxis or contusion: unexplained nosebleeds or bruising	✓		
Seizures (fits): loss of consciousness with uncontrollable shaking			✓
Heart attack: severe, crushing chest pain that can radiate into the arm and/ or jaw, palpitations, shortness of breath, nausea, vomiting, sweating			✓
Intestinal ischemia (blood flow to your intestines decreases due to a narrowed or blocked blood vessel): sudden or worsening abdominal pain (usually severe), urgent need to have a bowel movement, frequent, forceful bowel movements, nausea, vomiting, diarrhea, blood in your stool, confusion in older adults			✓
New Psychotic or Manic Symptoms: Paranoia, delusions **Hallucinations:** Seeing, feeling or hearing things that are not real **Mania:** feeling unusually excited, over-active, or uninhibited, picking of skin		✓	
Serious Skin Conditions (Steven's Johnson Syndrome, Toxic Epidermal Necrolysis): Swelling of the skin or serious skin rash seen as severe blisters of the skin and mucous membranes			✓
Serotonin Toxicity (also known as Serotonin Syndrome): agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			✓
Stroke: weakness, trouble speaking, vision problems, headache, dizziness			✓
Suicidal Behavior: Thoughts or actions about hurting or killing yourself			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store DYANAVEL XR in the original container at room temperature (15°C - 30°C).

Always keep DYANAVEL XR in a safe place to prevent theft, misuse or accidental exposure.

Keep out of reach and sight of children.

Discard any unused portion after 40 days of receiving the product. DYANAVEL XR should never be thrown into household trash, where children and pets may find it. Return any unused or expired medication to a pharmacy for proper disposal.

If you want more information about DYANAVEL XR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug- products/drug-product-database.html); the manufacturer's website www.kyepharma.com, or by calling 1-888-822-7126.

This leaflet was prepared by Kye Pharmaceuticals Inc.

Date of Authorization: 2025-07-28

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

DYANAVEL® XR

Amphetamine Extended-Release Tablets

This Patient Medication Information is written for the person who will be taking **DYANAVEL XR** Tablets. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **DYANAVEL XR** Tablets, talk to a healthcare professional.

Serious warnings and precautions box

- **Like other stimulants, the use of DYANAVEL XR may lead to abuse, misuse or dependence. This means you may feel like you need to take more of it over time, or that it would be difficult for you to stop taking it. If you think this is happening to you, talk to your healthcare professional.**
- **Misusing DYANAVEL XR may cause serious heart problems and even sudden death.**

What DYANAVEL XR is used for:

- Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 to 12 years of age and adults (18 years of age and older).

How DYANAVEL XR works:

DYANAVEL XR is an amphetamine that belongs to group of medicines called central nervous system stimulants. It works by changing the levels of certain chemicals in the brain. This helps to increase attention and decrease impulsivity and hyperactivity in patients with ADHD.

The ingredients in DYANAVEL XR are:

Medicinal ingredients: Amphetamine (as amphetamine (complexed with sodium polystyrene sulfonate), dextroamphetamine sulfate and amphetamine aspartate).

Non-medicinal ingredients: Citral, crospovidone, d-limonene, ethyl acetate, ethyl alcohol, ethyl butyrate, eugenol, gamma methyl ionone, guar gum, isoamyl acetate, iso-amyl butyrate, iso-butyl acetate, magnesium stearate, mannitol, microcrystalline cellulose, modified corn starch, orange oil, polyvinyl acetate, povidone, silicon dioxide, sodium lauryl sulfate, sodium polystyrene sulfonate, sucralose, talc, tangerine oil, triacetin, vanillin, and xanthan gum.

DYANAVEL XR comes in the following dosage forms:

Tablets: 5 mg (scored), 10 mg, 15 mg and 20 mg

Do not use DYANAVEL XR if you:

- Are allergic to amphetamine, or any of the ingredients in DYANAVEL XR
- Are sensitive, or allergic to any other stimulant medications (these may include cold or

allergy medications, or other medications used to treat ADHD)

- Are taking or have taken within the past 14 days a type of anti-depression medicine called a monoamine oxidase inhibitor (MAOI)
- Have symptoms of heart disease
- Have moderate to severe high blood pressure
- Have a condition that hardens the arteries
- Have hyperthyroidism (a condition that causes the thyroid gland to make too much of a hormone), or a condition called thyrotoxicosis
- Have glaucoma, an eye disease
- Have any condition that causes anxious or distressful feelings
- Have ever had any problems with drug or alcohol use (e.g., drinking too much, feeling like you cannot quit etc.)
- Have a condition called pheochromocytoma (a rare tumour that usually grows in the adrenal glands, above your kidneys)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DYANAVEL XR. Talk about any health conditions or problems you may have, including if you:

- Have structural heart abnormalities, symptoms of heart disease, a heart defect, serious heart rhythm problems, or other serious heart problems
- Have a family history of sudden cardiac death, or death related to heart problems
- Have mild high blood pressure
- Have mental health problems or a family history of mental health problems, including anxiety, psychosis, mania, bipolar illness, depression, aggression or suicide
- Have a disorder that affects the blood vessels outside your heart and brain. This includes a condition called “Raynaud’s phenomenon” (a condition that causes fingers and toes to feel numb, tingle and change colour when cold)
- Have a history of seizures (convulsions or epilepsy) or abnormal EEGs (measure of brainwave activity)
- Are involved in any physical exercises that are tiring on the body
- Consume alcohol
- Have or have a family history of motion tics, verbal tics, or Tourette’s syndrome
- Take other drugs for the treatment of ADHD
- Have kidney problems or are on dialysis
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed. DYANAVEL XR passes into your breast milk. You and your healthcare professional should decide if you will take DYANAVEL XR or breastfeed

Other warnings you should know about:

Serotonin toxicity (also known as Serotonin Syndrome): DYANAVEL XR may cause serotonin syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take DYANAVEL XR with other serotonergic drugs such as antidepressant or migraine medications.

Serotonin toxicity symptoms include:

- Fever, sweating, shivering, diarrhea, nausea, vomiting
- Muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination
- Fast heartbeat, changes in blood pressure
- Confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, coma

Heart related problems: The following heart related problems have been reported in people taking medicine like DYANAVEL XR, to treat ADHD:

- Sudden death in patients who have heart problems or heart defects
- Stroke and heart attack
- Increased blood pressure and heart rate

Sudden death has been reported in children and adolescents treated with drugs for ADHD. Those children and adolescents had problems with the structure of their heart or had other serious heart problems. DYANAVEL XR generally should not be used in patients who have any serious heart diseases or conditions, such as

- high blood pressure
- problems with the structure of their heart
- diseases that impact the muscles of their heart
- serious problems with their heartbeat

Seek immediate medical help if you have any signs of heart problems such as chest pain, shortness of breath, or fainting while taking DYANAVEL XR.

Mental health problems: The following mental health problems have been reported in people taking medicines like DYANAVEL XR, to treat ADHD:

- New or worse thoughts or feelings related to suicide (thinking about or feeling like killing yourself) and suicide attempt
- New or worse bipolar disorder (extreme mood swings, alternating from feelings of unusual excitement, over-active or un-inhibited, to feelings of depression, sadness, worthlessness or hopelessness)
- New or worsening aggressive behavior, anxiety, agitation or hostility
- New symptoms of psychosis (such as hearing voices, believing things that are not true, being suspicious)

These mental health problems are more likely to happen if you have known or unknown mental health conditions. These symptoms can happen at any time during treatment but are more likely to occur when you first start taking DYANAVEL XR, when the dose changes, or after stopping DYANAVEL XR treatment.

If you experience any new or worsening mental health symptoms while taking DYANAVEL XR, talk to your healthcare professional right away.

Dependence and tolerance: Like other stimulants, DYANAVEL XR has the potential to be abused if not taken correctly. This can lead you to becoming dependent on DYANAVEL XR or feeling like you need to take more of it over time (tolerance). If you have a history of problems with drug or alcohol use (substance use disorder), discuss this with your healthcare professional.

Stopping your treatment: Do NOT change your dose or stop taking DYANAVEL XR without discussing it with your healthcare professional first. Stopping your treatment abruptly may lead to serious side effects like depression, fatigue, stomach cramps, irritability and sleeping problems. If you need to stop taking DYANAVEL XR, careful supervision by a healthcare professional is needed. To avoid side effects, your healthcare professional will work with you to slowly taper you off DYANAVEL XR.

Growth and weight loss in children: Stimulants are believed to temporarily slow growth in children. They may also lead to a higher risk of weight loss in younger children. Your child's healthcare professional will be monitoring your child's height and weight while they are taking DYANAVEL XR. If your child is not growing or gaining weight as your healthcare professional expects, your healthcare professional may stop DYANAVEL XR treatment.

Testing and check-ups: your healthcare professional may do tests before you start, and during your treatment with DYANAVEL XR. These tests may include:

- Tests that check for problems in the heart or brain
- Tests that check blood pressure and heart rate
- Blood tests to check complete blood count, platelet counts and liver enzymes

Driving or doing tasks that require special attention: DYANAVEL XR can affect your ability to perform certain tasks such as driving or using tools or machinery. Avoid doing tasks that require special attention until you know how you respond to DYANAVEL XR.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions:

Do NOT take DYANAVEL XR if you:

- are taking, or have recently taken (in the last 14 days), a type of anti-depression medicine called a monoamine oxidase inhibitor (MAOI). If you are unsure, ask your healthcare professional.

The following may also interact with DYANAVEL XR:

- other central nervous system stimulants
- alcohol
- medicines used to treat depression including St. John's Wort, selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs)
- medicines used to treat migraines, called triptans

- medicines that make urine or digestive contents more acidic (e.g., guanethidine, reserpine, ascorbic acid, ammonium chloride, sodium acid phosphate)
- medicines that make urine or digestive contents more alkaline (e.g., acetazolamide, thiazides, sodium bicarbonate, antacids)
- medicines used to reduce or increase blood pressure
- medicines used to prevent blood clots (commonly called “blood thinners”)
- cold and allergy medicines
- antipsychotic medicines (e.g., chlorpromazine, haloperidol)
- lithium
- methenamine therapy
- opioid pain medicines (e.g., meperidine, propoxyphene)
- seizure medicines (e.g., ethosuximide, phenobarbital, phenytoin)
- medicines used to block the action of epinephrine and norepinephrine
- products known as veratrum alkaloids
- medicines known as ‘proton pump inhibitors’, these reduce the amount of acid in your stomach (e.g., omeprazole)

While on DYANAVEL XR, do not start taking a new medicine or herbal remedy before checking with your healthcare professional.

How to take DYANAVEL XR:

- Take DYANAVEL XR exactly as prescribed. Your healthcare professional may adjust the dose, if needed, until it is right for you. During dose adjustment, you may still have ADHD symptoms.
- Take DYANAVEL XR one time each day in the morning. DYANAVEL XR is an extended-release medicine, meaning the medicine releases into your body throughout the day.
- DYANAVEL XR can be taken with or without food.
- From time to time, your healthcare professional may stop DYANAVEL XR treatment for a while to check ADHD symptoms.

Usual dose:

Your healthcare professional will determine the best dose to treat your symptoms.

Overdose:

If you think you, or a person you are caring for, have taken too much DYANAVEL XR, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada’s toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If a dose of DYANAVEL XR is missed, wait until the next day and take the usual dose at the usual time in the morning. Do not take an afternoon dose. Do not double the dose to make up for the missed dose.

Possible side effects from using DYANAVEL XR:

These are not all the possible side effects you may have when taking DYANAVEL XR. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Behavioural changes (anxiety, irritability, mood swings, nervousness)
- Chills
- Decrease or loss of appetite
- Difficulty falling asleep
- Digestive problems (constipation, diarrhea, indigestion, nausea, vomiting)
- Dizziness
- Drowsiness
- Dry mouth and thirst
- Fever
- Grinding of teeth
- Headache
- Neck pain
- Reduced sexual drive
- Sensitivity to light
- Stomach ache
- Sweating
- Unpleasant taste
- Weight loss

Serious side effects and what to do about them

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Common			
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Cardiomyopathy (signs of heart muscle disease): breathlessness or swelling of the legs		✓	

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Depression: feeling sad, loss of interest in usual activities, hopelessness, insomnia or sleeping too much		✓	
Dyspnea: Shortness of breath			✓
Fungal Infection		✓	
Heart palpitations or fast heart beat: skipping beats, beating too fast, pounding, fluttering rapidly		✓	
New Tics: hard to control motion tics (repeat twitching of any parts of the body) or verbal tics (repeating of sounds or words)		✓	
Urinary Tract Infection (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		✓	
Uncommon			
Aggressive Behavior, Anger or Hostility		✓	
High Blood Pressure: headaches, dizziness, lightheadedness, ringing in the ears, fainting		✓	
Trouble with vision: eyesight changes or blurred vision		✓	
Unknown			
Condition Resembling Raynaud's Phenomenon: discoloration of the hands and feet, pain, sensations of cold and/ or numbness		✓	
Epistaxis or contusion: unexplained nosebleeds or bruising	✓		
Seizures (fits): loss of consciousness with uncontrollable shaking			✓
Heart attack: severe, crushing chest pain that can radiate into the arm and/ or jaw, palpitations, shortness of breath, nausea, vomiting, sweating			✓
Intestinal ischemia (blood flow to your intestines decreases due to a narrowed or blocked blood vessel): sudden or worsening abdominal pain (usually severe), urgent need to have a bowel movement, frequent, forceful bowel movements, nausea, vomiting, diarrhea, blood in your stool, confusion in older adults			✓

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
New Psychotic or Manic Symptoms: Paranoia, delusions **Hallucinations:** Seeing, feeling or hearing things that are not real **Mania:** feeling unusually excited, over-active, or uninhibited, picking of skin		✓	
Serious Skin Conditions (Steven's Johnson Syndrome, Toxic Epidermal Necrolysis): Swelling of the skin or serious skin rash seen as severe blisters of the skin and mucous membranes			✓
Serotonin Toxicity (also known as Serotonin Syndrome): agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			✓
Stroke: weakness, trouble speaking, vision problems, headache, dizziness			✓
Suicidal Behavior: Thoughts or actions about hurting or killing yourself			✓

If you or your child have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your or your child's healthcare professional.

Reporting Side Effects

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Storage:

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