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

ARYNTA™ (lisdexamfetamine dimesylate) Oral Solution, CII
Initial U.S. Approval: 2007

WARNING: ABUSE, MISUSE, AND ADDICTION

See full prescribing information for complete boxed warning.

ARYNTA has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including ARYNTA, can result in overdose and death (5.1, 9.2, 10):

- **Before prescribing ARYNTA, assess each patient's risk for abuse, misuse, and addiction.**
- **Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug.**
- **Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction.**

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

ARYNTA is a central nervous system (CNS) stimulant indicated for the treatment of (1):

- Attention Deficit Hyperactivity Disorder (ADHD) in adults and pediatric patients 6 years and older.
- Moderate to severe binge eating disorder (BED) in adults

Limitations of Use:

- Pediatric patients with ADHD younger than 6 years of age experienced more long-term weight loss than patients 6 years and older. (8.4)
- ARYNTA is not indicated for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of ARYNTA for the treatment of obesity have not been established (5.2)

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

Indicated Population	Initial Dose	Titration Schedule	Recommended Dose	Maximum Dose
ADHD (Adults and pediatric patients 6 years and older) (2.2)	30 mg every morning	10 mg or 20 mg weekly	30 mg to 70 mg per day	70 mg per day
BED (Adults) (2.3)	30 mg every morning	20 mg weekly	50 mg to 70 mg per day	70 mg per day

- Prior to treatment, assess for presence of cardiac disease (2.4)
- Severe renal impairment: Maximum dose is 50 mg/day (2.5)
- End stage renal disease (ESRD): Maximum dose is 30 mg/day (2.5)

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

Oral solution: 10 mg/mL.

----------CONTRAINDICATIONS----------

- Known hypersensitivity to amphetamine products or other ingredients in ARYNTA (4)
- Use with monoamine oxidase (MAO) inhibitor, or within 14 days of the last MAO inhibitor dose (4, 7.1)

----------WARNINGS AND PRECAUTIONS----------

- *Risks to Patients with Serious Cardiac Disease:* Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease (5.2)
- *Increased Blood Pressure and Heart Rate:* Monitor blood pressure and pulse (5.3)
- *Psychiatric Adverse Reactions:* Prior to initiating ARYNTA, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing ARYNTA (5.4)
- *Long-Term Suppression of Growth in Pediatric Patients:* Closely monitor growth (height and weight) in pediatric patients. Pediatric patients not growing or gaining height or weight as expected may need to have their treatment interrupted (5.5)
- *Peripheral Vasculopathy, including Raynaud's phenomenon:* Careful observation for digital changes is necessary during ARYNTA treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy (5.6)
- *Serotonin Syndrome:* Increased risk when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. If it occurs, discontinue ARYNTA and initiate supportive treatment (4, 5.7, 10)
- *Motor and Verbal Tics, and Worsening of Tourette's Syndrome:* Before initiating ARYNTA, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome. Discontinue treatment if clinically appropriate (5.8)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) in pediatric patients ages 6 to 17 years, and/or adults with ADHD were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting (6.1)
Most common adverse reactions (incidence ≥ 5% and at a rate at least twice placebo) in adults with BED were dry mouth, insomnia, decreased appetite, increased heart rate, constipation, feeling jittery, and anxiety (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Azurity Pharmaceuticals, Inc., at 1-800-461-7449 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Acidifying and Alkalinizing Agents: Agents that alter urinary pH can alter blood levels of amphetamine.
Acidifying agents decrease amphetamine blood levels, while alkalinizing agents increase amphetamine blood levels. Adjust ARYNTA dosage accordingly (2.6, 7.1)

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* May cause fetal harm (8.1)
- *Lactation:* Breastfeeding not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2025

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE, MISUSE, AND ADDICTION

ARYNTA has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including ARYNTA, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.
Before prescribing ARYNTA, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug. Throughout ARYNTA treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2)]*.

1 INDICATIONS AND USAGE

ARYNTA is indicated for the treatment of:

- Attention Deficit Hyperactivity Disorder (ADHD) in adults and pediatric patients 6 years and older *[see Clinical Studies (14.1)]*.
- Moderate to severe binge eating disorder (BED) in adults *[see Clinical Studies (14.2)]*.

Limitations of Use:

- Pediatric patients with ADHD younger than 6 years of age experienced more long-term weight loss than patients 6 years and older *[see Use in Specific Populations (8.4)]*.
- ARYNTA is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of ARYNTA for the treatment of obesity have not been established *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating patients with ARYNTA, assess:

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

2.2 General Administration Information

Take ARYNTA orally in the morning with or without food; avoid afternoon doses because of the potential for insomnia.

Instruct caregivers/patients to read the ‘Instructions for Use’ for complete administration instructions.

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- Use the oral dosing syringe and bottle adapter provided with ARYNTA.
- Ensure that the bottle adapter is firmly inserted into the bottle before first use and keep the adapter in place for the duration of the usage of the bottle.
- Throw away (discard) any remaining ARYNTA 30 days after first opening the bottle.

2.3 Dosage for Treatment of ADHD

The recommended starting dosage in adults and pediatric patients 6 years and older is 30 mg once daily in the morning. Dosage may be adjusted in increments of 10 mg or 20 mg at approximately weekly intervals up to maximum recommended dosage of 70 mg once daily *[see Clinical Studies (14.1)]*.

2.4 Dosage for Treatment of Moderate to Severe BED in Adults

The recommended starting dosage in adults is 30 mg once daily to be titrated in increments of 20 mg at approximately weekly intervals to achieve the recommended target dose of 50 mg to 70 mg once daily. The maximum recommended dosage is 70 mg once daily *[see Clinical Studies (14.2)]*. Discontinue ARYNTA if binge eating does not improve.

2.5 Dosage in Patients with Renal Impairment

In patients with severe renal impairment (GFR 15 to < 30 mL/min/1.73 m^2), the maximum dosage should not exceed 50 mg once daily. In patients with end stage renal disease (ESRD, GFR < 15 mL/min/1.73 m^2), the maximum recommended dosage is 30 mg once daily *[see Use in Specific Populations (8.6)]*.

2.6 Dosage Modifications due to Drug Interactions

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

3 DOSAGE FORMS AND STRENGTHS

ARYNTA oral solution 10 mg/mL is supplied as a clear colorless solution.

4 CONTRAINDICATIONS

ARYNTA is contraindicated in patients with:

- Known hypersensitivity to amphetamine products or other ingredients of ARYNTA. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have been observed in postmarketing reports *[see Adverse Reactions (6.2)]*.
- Patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis *[see Warnings and Precautions (5.7) and Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Abuse, Misuse, and Addiction

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

Before prescribing ARYNTA, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks and proper disposal of any unused drug. Advise patients to store ARYNTA in a safe place, preferably locked, and instruct patients to not give ARYNTA to anyone else. Throughout ARYNTA treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

5.2 Risks to Patients with Serious Cardiac Disease

Sudden death has been reported in patients with structural cardiac abnormalities or other serious cardiac disease who were treated with CNS stimulants at the recommended ADHD dosage. Avoid ARYNTA use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac disease.

5.3 Increased Blood Pressure and Heart Rate

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

Monitor all ARYNTA -treated patients for potential tachycardia and hypertension.

5.4 Psychiatric Adverse Reactions

<u>Exacerbation of Pre-existing Psychosis</u>

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

<u>Induction of a Manic Episode in Patients with Bipolar Disorder</u>

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

<u>New Psychotic or Manic Symptoms</u>

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

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treated patients compared to 0% of placebo-treated patients. If such symptoms occur, consider discontinuing ARYNTA.

5.5 Long-Term Suppression of Growth in Pediatric Patients

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients.

In a 4-week, placebo-controlled trial of ARYNTA in pediatric patients ages 6 to 12 years old with ADHD, there was a dose-related decrease in weight in the ARYNTA groups compared to weight gain in the placebo group. Additionally, in studies of another stimulant, there was slowing of the increase in height *[see Adverse Reactions (6.1)]*.

Closely monitor growth (weight and height) in ARYNTA -treated pediatric patients. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted. ARYNTA is not approved for use in pediatric patients below 6 years of age *[see Use in Specific Populations (8.4)]*.

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

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

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

5.7 Serotonin Syndrome

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

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus,

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hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

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

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

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

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

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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Attention Deficit Hyperactivity Disorder

The safety data in this section is based on data from the 4-week controlled parallel-group clinical studies of Lisdexamfetamine Dimesylate in pediatric and adult patients with ADHD *[see Clinical Studies (14.1)]*.

Adverse Reactions Associated with Discontinuation of Treatment in ADHD Clinical Trials

In the controlled trial in pediatric patients ages 6 to 12 years (Study 1), 8% (18/218) of ARYNTA-treated patients discontinued due to adverse reactions compared to 0% (0/72) of placebo-treated patients. The most frequently reported adverse reactions (1% or more and twice rate of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, decreased appetite and rash [2 instances for each adverse reaction, i.e., 2/218 (1%)]. Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) included abdominal pain upper, dry mouth, weight decreased, dizziness, somnolence, logorrhea, chest pain, anger and hypertension.

In the controlled trial in pediatric patients ages 13 to 17 years (Study 4), 3% (7/233) of ARYNTA treated patients discontinued due to adverse reactions compared to 1% (1/77) of placebo-treated patients. The most frequently reported adverse reactions (1% or more and twice rate of placebo) were decreased appetite (2/233; 1%) and insomnia (2/233; 1%). Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) included irritability, dermatillomania, mood swings, and dyspnea.

In the controlled adult trial (Study 7), 6% (21/358) of ARYNTA -treated patients discontinued due to adverse reactions compared to 2% (1/62) of placebo-treated patients. The most frequently reported adverse reactions (1% or more and twice rate of placebo) were insomnia (8/358; 2%), tachycardia (3/358; 1%), irritability (2/358; 1%), hypertension (4/358; 1%), headache (2/358; 1%), anxiety (2/358; 1%), and dyspnea (3/358; 1%). Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) included palpitations, diarrhea, nausea, decreased appetite, dizziness, agitation, depression, paranoia and restlessness.

Adverse Reactions Occurring at an Incidence of ≥5% or More Among ARYNTA Treated Patients with ADHD in Clinical Trials

The most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in pediatric patients ages 6 to 17 years, and/or adults were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.

Adverse Reactions Occurring at an Incidence of 2% or More Among ARYNTA Treated Patients with ADHD in Clinical Trials

Adverse reactions reported in the controlled trials in pediatric patients ages, 6 to 12 years (Study 1), pediatric patients ages 13 to 17 years (Study 4), and adult patients (Study 7) treated with ARYNTA or placebo are presented in Tables 1, 2 and 3 below.

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Table 1. Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 6 to 12 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 1)

	Lisdexamfetamine Dimesylate (n=218)	**Placebo (n=72)**
Decreased Appetite	39%	4%
Insomnia	22%	3%
Abdominal Pain Upper	12%	6%
Irritability	10%	0%
Vomiting	9%	4%
Weight Decreased	9%	1%
Nausea	6%	3%
Dry Mouth	5%	0%
Dizziness	5%	0%
Affect lability	3%	0%
Rash	3%	0%
Pyrexia	2%	1%
Somnolence	2%	1%
Tic	2%	0%
Anorexia	2%	0%

Table 2. Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 13 to 17 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 4)

	Lisdexamfetamine Dimesylate (n=233)	**Placebo (n=77)**
Decreased Appetite	34%	3%
Insomnia	13%	4%
Weight Decreased	9%	0%
Dry Mouth	4%	1%
Palpitations	2%	1%
Anorexia	2%	0%
Tremor	2%	0%

Table 3. Adverse Reactions Reported by 2% or More of Adult Patients with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4- Week Clinical Trial (Study 7)

	Lisdexamfetamine Dimesylate (n=358)	**Placebo (n=62)**
Decreased Appetite	27%	2%

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Insomnia	27%	8%
Dry Mouth	26%	3%
Diarrhea	7%	0%
Nausea	7%	0%
Anxiety	6%	0%
Anorexia	5%	0%
Feeling Jittery	4%	0%
Agitation	3%	0%
Increased Blood Pressure	3%	0%
Hyperhidrosis	3%	0%
Restlessness	3%	0%
Decreased Weight	3%	0%
Dyspnea	2%	0%
Increased Heart Rate	2%	0%
Tremor	2%	0%
Palpitations	2%	0%

In addition, in the adult population erectile dysfunction was observed in 2.6% of males on lisdexamfetamine dimesylate and 0% on placebo; decreased libido was observed in 1.4% of subjects on lisdexamfetamine dimesylate and 0% on placebo.

Weight Loss and Slowing Growth Rate in Pediatric Patients with ADHD

In a controlled trial of lisdexamfetamine dimesylate in pediatric patients ages 6 to 12 years (Study 1), mean weight loss from baseline after 4 weeks of therapy was -0.9, -1.9, and -2.5 pounds, respectively, for patients receiving 30 mg, 50 mg, and 70 mg of lisdexamfetamine dimesylate, compared to a 1 pound weight gain for patients receiving placebo. Higher doses were associated with greater weight loss with 4 weeks of treatment. Careful follow-up for weight in pediatric patients ages 6 to 12 years who received lisdexamfetamine dimesylate over 12 months suggests that consistently medicated pediatric patients (i.e., treatment for 7 days per week throughout the year) have a slowing in growth rate, measured by body weight as demonstrated by an age- and sex-normalized mean change from baseline in percentile, of -13.4 over 1 year (average percentiles at baseline and 12 months were 60.9 and 47.2, respectively).

In a 4-week controlled trial of lisdexamfetamine dimesylate in pediatric patients ages 13 to 17 years, mean weight loss from baseline to endpoint was -2.7, -4.3, and -4.8 lbs., respectively, for patients receiving 30 mg, 50 mg, and 70 mg of lisdexamfetamine dimesylate, compared to a 2.0 pound weight gain for patients receiving placebo.

Careful follow-up of weight and height in pediatric patients ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as we l as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated pediatric patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated pediatric patients ages 7 to 13 years (i.e., treatment for 7 days per week throughout the

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year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. In a controlled trial of amphetamine (d- to l-enantiomer ratio of 3:1) in pediatric patients ages 13 to 17 years, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 pounds and -2.8 pounds, respectively, for patients receiving 10 mg and 20 mg of amphetamine. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment *[see Warnings and Precautions (5.5)]*.

Weight Loss in Adults with ADHD

In the controlled adult trial (Study 7), mean weight loss after 4 weeks of therapy was 2.8 pounds, 3.1 pounds, and 4.3 pounds, for patients receiving final doses of 30 mg, 50 mg, and 70 mg of lisdexamfetamine dimesylate, respectively, compared to a mean weight gain of 0.5 pounds for patients receiving placebo.

Binge Eating Disorder

The safety data in this section is based on data from two 12-week parallel group, flexible-dose, placebo-controlled studies in adults with BED *[see Clinical Studies 14.2]*. Patients with cardiovascular risk factors other than obesity and smoking were excluded.

Adverse Reactions Associated with Discontinuation of Treatment in BED Clinical Trials

In controlled trials of patients ages 18 to 55 years, 5.1% (19/373) of lisdexamfetamine dimesylate -treated patients discontinued due to adverse reactions compared to 2.4% (9/372) of placebo-treated patients. No single adverse reaction led to discontinuation in 1% or more of lisdexamfetamine dimesylate -treated patients. Less commonly reported adverse reactions (less than 1% or less than twice rate of placebo) included increased heart rate, headache, abdominal pain upper, dyspnea, rash, insomnia, irritability, feeling jittery and anxiety.

Adverse Reactions Occurring at an Incidence of 5% or More and At Least Twice Placebo Among Lisdexamfetamine Dimesylate Treated Patients with BED in Clinical Trials

The most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in adults were dry mouth, insomnia, decreased appetite, increased heart rate, constipation, feeling jittery, and anxiety.

Adverse Reactions Occurring at an Incidence of 2% or More and At Least Twice Placebo Among Lisdexamfetamine Dimesylate Treated Patients with BED in Clinical Trials

Adverse reactions reported in the pooled controlled trials in adult patients (Study 11 and 12) treated with lisdexamfetamine dimesylate or placebo are presented in Table 4 below.

Table 4. Adverse Reactions Reported by 2% or More of Adult Patients with BED Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in 12-Week Clinical Trials (Study 11 and 12)

	Lisdexamfetamine dimesylate (n=373)	**Placebo (n=372)**
Dry Mouth	36%	7%
Insomnia*	20%	8%

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Decreased Appetite	8%	2%
Increased Heart Rate†	7%	1%
Feeling Jittery	6%	1%
Constipation	6%	1%
Anxiety	5%	1%
Diarrhea	4%	2%
Decreased Weight	4%	0%
Hyperhidrosis	4%	0%
Vomiting	2%	1%
Gastroenteritis	2%	1%
Paresthesia	2%	1%
Pruritus	2%	1%
Upper Abdominal Pain	2%	0%
Energy Increased	2%	0%
Urinary Tract Infection	2%	0%
Nightmare	2%	0%
Restlessness	2%	0%
Oropharyngeal Pain	2%	0%

*Includes all preferred terms containing the word "insomnia."
†Includes the preferred terms "heart rate increased "and "tachycardia."

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of lisdexamfetamine dimesylate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events are as follows: cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, dysgeusia, motor and verbal tics, bruxism, depression, dermatillomania, alopecia, aggression, Stevens-Johnson Syndrome, chest pain, angioedema, urticaria, seizures, libido changes, frequent or prolonged erections, constipation, rhabdomyolysis, and intestinal ischemia.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Amphetamines

Table 5. Drugs Having Clinically Important Interactions with Amphetamines

MAO Inhibitors (MAOI)	
Prevention or Management	Do not administer ARYNTA during or within 14 days following the administration of MAOI [*see Contraindications (4)*].

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Mechanism and Clinical Effect(s)	MAOI antidepressants slow amphetamine metabolism, increasing amphetamines effect on the release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of hypertensive crisis. Toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Serotonergic Drugs	
Prevention or Management	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome, particularly during ARYNTA initiation or dosage increase. If serotonin syndrome occurs, discontinue ARYNTA and the concomitant serotonergic drug(s) [*see Warnings and Precautions (5.7)*].
Mechanism and Clinical Effect(s)	The concomitant use of lisdexamfetamine dimesylate and serotonergic drugs increases the risk of serotonin syndrome.
CYP2D6 Inhibitors	
Prevention or Management	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during ARYNTA initiation and after a dosage increase. If serotonin syndrome occurs, discontinue ARYNTA and the CYP2D6 inhibitor [*see Warnings and Precautions (5.7) and Overdosage (10)*].
Mechanism and Clinical Effect(s)	The concomitant use of lisdexamfetamine dimesylate and CYP2D6 inhibitors may increase the exposure of dextroamphetamine, the active metabolite of lisdexamfetamine dimesylate compared to the use of the drug alone and increase the risk of serotonin syndrome.
Alkalinizing Agents	
Prevention or Management	Co-administration of ARYNTA and urinary alkalinizing agents should be avoided.
Mechanism and Clinical Effect(s)	Urinary alkalinizing agents can increase blood levels and potentiate the action of amphetamine.
Acidifying Agents	
Prevention or Management	Increase dose based on clinical response.
Mechanism and Clinical Effect(s)	Urinary acidifying agents can lower blood levels and efficacy of amphetamines.
Tricyclic Antidepressants	
Prevention or Management	Monitor frequently and adjust or use alternative therapy based on clinical response.
Mechanism and Clinical Effect(s)	May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the

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	concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visiting online at https://womensmentalhealth.org/clinical-and researchprograms/pregnancyregistry/adhdmedications/.

Risk Summary

The limited available data from published literature and postmarketing reports on use of ARYNTA in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines [*see Clinical Considerations*]. In animal reproduction studies, lisdexamfetamine dimesylate (a prodrug of d-amphetamine) had no effects on embryofetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis. Pre- and postnatal studies were not conducted with lisdexamfetamine dimesylate. However, amphetamine (d- to l- ratio of 3:1) administration to pregnant rats during gestation and lactation caused a decrease in pup survival and a decrease in pup body weight that correlated with a delay in developmental landmarks at clinically relevant doses of amphetamine. In addition, adverse effects on reproductive performance were observed in pups whose mothers were treated with amphetamine. Long-term neurochemical and behavioral effects have also been reported in animal developmental studies using clinically relevant doses of amphetamine [*see Data*].

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Amphetamines, such as ARYNTA, cause vasoconstriction and thereby may decrease placental perfusion. In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. Infants born to amphetamine-dependent mothers have an increased risk of premature delivery and low birth weight.

Monitor infants born to mothers taking amphetamines for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness.

Data

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Animal Data

Lisdexamfetamine dimesylate had no apparent effects on embryo-fetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 40 and 120 mg/kg/day, respectively. These doses are approximately 5.5 and 33 times, respectively, the maximum recommended human dose (MRHD) of 70 mg/day given to adults, on a mg/m^2 body surface area basis.

A study was conducted with amphetamine (d- to l- enantiomer ratio of 3:1) in which pregnant rats received daily oral doses of 2, 6, and 10 mg/kg from gestation day 6 to lactation day 20. All doses caused hyperactivity and decreased weight gain in the dams. A decrease in pup survival was seen at all doses. A decrease in pup body weight was seen at 6 and 10 mg/kg which correlated with delays in developmental landmarks, such as preputial separation and vaginal opening. Increased pup locomotor activity was seen at 10 mg/kg on day 22 postpartum but not at 5 weeks postweaning. When pups were tested for reproductive performance at maturation, gestational weight gain, number of implantations, and number of delivered pups were decreased in the group whose mothers had been given 10 mg/kg.

A number of studies from the literature in rodents indicate that prenatal or early postnatal exposure to amphetamine (*d*- or *d*, *l*-) at doses similar to those used clinically can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

8.2 Lactation

Risk Summary

Lisdexamfetamine is a pro-drug of dextroamphetamine. Based on limited case reports in published literature, amphetamine (*d*-or *d*, *l*-) is present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. It is possible that large dosages of dextroamphetamine might interfere with milk production, especially in women whose lactation is not well established.

Because of the potential for serious adverse reactions in nursing infants, including serious cardiovascular reactions, blood pressure and heart rate increase, suppression of growth, and peripheral vasculopathy, advise patients that breastfeeding is not recommended during treatment with ARYNTA.

8.4 Pediatric Use

ADHD

Safety and effectiveness of ARYNTA have been established in pediatric patients with ADHD ages 6 to 17 years *[see Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)]*.

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Safety and effectiveness of ARYNTA have not been established in pediatric patients below the age of 6 years.

Safety and efficacy of lisdexamfetamine dimesylate were evaluated in a double-blind, randomized, parallel-group, placebo-controlled, fixed-dose study in pediatric patients ages 4 to 5 years with ADHD, followed by a 1-year open-label extension study. In these studies, patients experienced elevated rates of adverse reactions, including weight loss, decreased BMI, decreased appetite, insomnia, infections (upper respiratory and nasopharyngitis), irritability, and affect lability.

With the same lisdexamfetamine dimesylate dose, mean steady state exposure of dextroamphetamine was approximately 44% higher in pediatric patients ages 4 to 5 years compared to the pediatric patients ages 6 to 11 years.

BED

Safety and effectiveness of ARYNTA have not been established in pediatric patients with BED less than 18 years of age.

Growth Suppression

Growth should be monitored during treatment with stimulants, including ARYNTA, and pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*.

Juvenile Animal Data

Studies conducted in juvenile rats and dogs at clinically relevant doses showed growth suppression that partially or fully reversed in dogs and female rats but not in male rats after a four-week drug-free recovery period.

A study was conducted in which juvenile rats received oral doses of 4, 10, or 40 mg/kg/day of lisdexamfetamine dimesylate from day 7 to day 63 of age. These doses are approximately 0.3, 0.7, and 3 times the maximum recommended human daily dose of 70 mg on a mg/m^2 basis for a child. Dose-related decreases in food consumption, bodyweight gain, and crown-rump length were seen; after a four-week drug-free recovery period, bodyweights and crown-rump lengths had significantly recovered in females but were still substantially reduced in males. Time to vaginal opening was delayed in females at the highest dose, but there were no drug effects on fertility when the animals were mated beginning on day 85 of age.

In a study in which juvenile dogs received lisdexamfetamine dimesylate for 6 months beginning at 10 weeks of age, decreased bodyweight gain was seen at all doses tested (2, 5, and 12 mg/kg/day, which are approximately 0.5, 1, and 3 times the maximum recommended human daily dose on a mg/m^2 basis for a child). This effect partially or fully reversed during a four-week drug-free recovery period.

8.5 Geriatric Use

Clinical studies of lisdexamfetamine dimesylate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience and pharmacokinetic data [*see Clinical Pharmacology (12.3)*] have

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not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

Due to reduced clearance in patients with severe renal impairment (GFR 15 to < 30 mL/min/1.73 m^2), the maximum dose should not exceed 50 mg/day. The maximum recommended dose in ESRD (GFR < 15 mL/min/1.73 m^2) patients is 30 mg/day *[see Clinical Pharmacology (12.3)]*.

Lisdexamfetamine and d-amphetamine are not dialyzable.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ARYNTA contains lisdexamfetamine, a prodrug of amphetamine, a Schedule II controlled substance.

9.2 Abuse

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

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

Misuse and abuse of lisdexamfetamine, a prodrug of amphetamine, may cause increased heart rate, respiratory rate, or blood pressure; sweating; dilated pupils; hyperactivity; restlessness; insomnia; decreased appetite; loss of coordination; tremors; flushed skin; vomiting; and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including ARYNTA, can result in overdose and death *[see Overdosage (10)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

<u>Studies of ARYNTA in Drug Abusers</u>

A randomized, double-blind, placebo-control, cross-over, abuse liability study in 38 patients with a history of drug abuse was conducted with single-doses of 50, 100, or 150 mg of lisdexamfetamine dimesylate, 40 mg of immediate-release d-amphetamine sulphate (a controlled II substance), and

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200 mg of diethylpropion hydrochloride (a controlled IV substance). lisdexamfetamine dimesylate 100 mg produced significantly less "Drug Liking Effects" as measured by the Drug Rating Questionnaire-Subject score, compared to d-amphetamine 40 mg; and 150 mg of lisdexamfetamine dimesylate demonstrated similar "Drug-Liking Effects" compared to 40 mg of d-amphetamine and 200 mg of diethylpropion.

Intravenous administration of 50 mg lisdexamfetamine dimesylate to individuals with a history of drug abuse produced positive subjective responses on scales measuring "Drug Liking", "Euphoria", "Amphetamine Effects", and "Benzedrine Effects" that were greater than placebo but less than those produced by an equivalent dose (20 mg) of intravenous d-amphetamine.

9.3 Dependence

Physical Dependence

ARYNTA may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal signs and symptoms after abrupt discontinuation or dose reduction following prolonged use of CNS stimulants including ARYNTA include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

Tolerance

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

10 OVERDOSAGE

Clinical Effects of Overdose

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

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

Overdose Management

Consider the possibility of multiple drug ingestion. The pharmacokinetic profile of ARYNTA should be considered when treating patients with overdose. Lisdexamfetamine and d-amphetamine are not dialyzable. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

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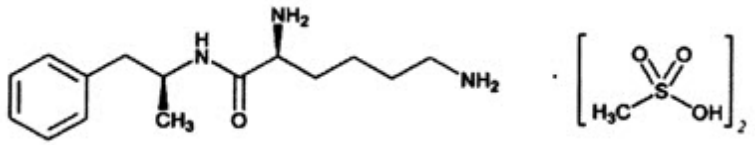
11 DESCRIPTION

ARYNTA (lisdexamfetamine dimesylate), is a CNS stimulant. The chemical designation for lisdexamfetamine dimesylate is (2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate. The molecular formula is $C_{15}H_{25}N_3O\cdot(CH_4O_3S)_2$, which corresponds to a molecular weight of 455.60.
The chemical structure is:



Lisdexamfetamine dimesylate is a white to off-white powder that is soluble in water (792 mg/mL). The pH is 4.24. The pKa values are 10.21 and 15.89.

ARYNTA oral solution is a clear colorless solution, contains 10 mg/mL of lisdexamfetamine dimesylate (equivalent to 5.8 mg of lisdexamfetamine). Inactive ingredients: dibasic sodium phosphate dihydrate, methylparaben sodium, monobasic sodium phosphate dihydrate, propylparaben sodium, propylene glycol, saccharin sodium, hydrochloric acid, sodium hydroxide and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lisdexamfetamine is a prodrug of dextroamphetamine. Amphetamines are noncatecholamine sympathomimetic amines with CNS stimulant activity. The exact mode of therapeutic action in ADHD and BED is not known.

12.2 Pharmacodynamics

Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*.

12.3 Pharmacokinetics

No clinically significant difference in lisdexamfetamine and dextroamphetamine exposures was observed following oral administration of either ARYNTA or lisdexamfetamine dimesylate capsule.

Pharmacokinetic studies after oral administration of lisdexamfetamine dimesylate have been conducted in healthy adult (capsule and chewable tablet formulations) and pediatric (6 to 12 years) patients with ADHD (capsule formulation). After single dose administration of lisdexamfetamine

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dimesylate, pharmacokinetics of dextroamphetamine was found to be linear between 30 mg and 70 mg in a pediatric study (6 to 12 years), and between 50 mg and 250 mg in an adult study. Dextroamphetamine pharmacokinetic parameters following administration of lisdexamfetamine dimesylate in adults exhibited low inter-subject (<25%) and intra-subject (<8%) variability. There is no accumulation of lisdexamfetamine and dextroamphetamine at steady state in healthy adults.

Absorption

Following single-dose administration of ARYNTA under fasted conditions, the peak plasma concentrations (Cmax) of lisdexamfetamine and dextroamphetamine were reached at approximately 1 hour and 3.5 hours post dose, respectively.

Effect of Food

No clinically significant differences in ARYNTA pharmacokinetics were observed following administration of a high-fat meal (1000 calories, 50% fat). Food delayed the median time to reach Cmax (Tmax) of dextroamphetamine from 3.5 hours to 4.5 hours.

Elimination

Plasma concentrations of unconverted lisdexamfetamine are low and transient, generally becoming non-quantifiable by 8 hours after administration. The plasma elimination half-life of lisdexamfetamine typically averaged less than one hour in volunteers ages 6 years and older. The plasma elimination half-life of dextroamphetamine was approximately 8.6 to 9.5 hours in pediatric patients 6 to 12 years and 10 to 11.3 hours in healthy adults.

Metabolism

Lisdexamfetamine is converted to dextroamphetamine and l-lysine primarily in blood due to the hydrolytic activity of red blood cells after oral administration of lisdexamfetamine dimesylate. *In vitro* data demonstrated that red blood cells have a high capacity for metabolism of lisdexamfetamine; substantial hydrolysis occurred even at low hematocrit levels (33% of normal). Lisdexamfetamine is not metabolized by cytochrome P450 enzymes.

Excretion

Following oral administration of a 70 mg dose of radiolabeled lisdexamfetamine dimesylate to 6 healthy subjects, approximately 96% of the oral dose radioactivity was recovered in the urine and only 0.3% recovered in the feces over a period of 120 hours. Of the radioactivity recovered in the urine, 42% of the dose was related to amphetamine, 25% to hippuric acid, and 2% to intact lisdexamfetamine.

Specific Populations

Exposures of dextroamphetamine in specific populations are summarized in Figure 1.

Figure 1. Specific Populations*:

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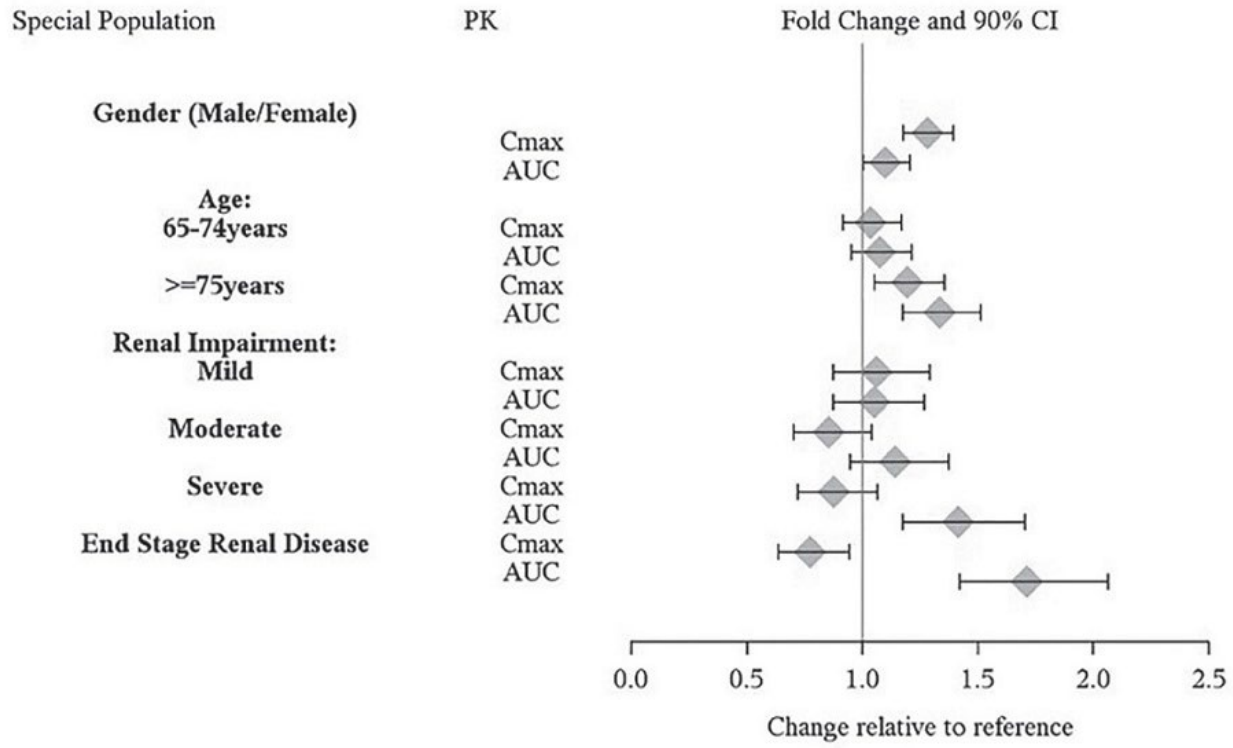

*Figure 1 shows the geometric mean ratios and the 90% confidence limits for C_{max} and AUC of d-amphetamine. Comparison for gender uses males as the reference. Comparison for age uses 55-64 years as the reference.

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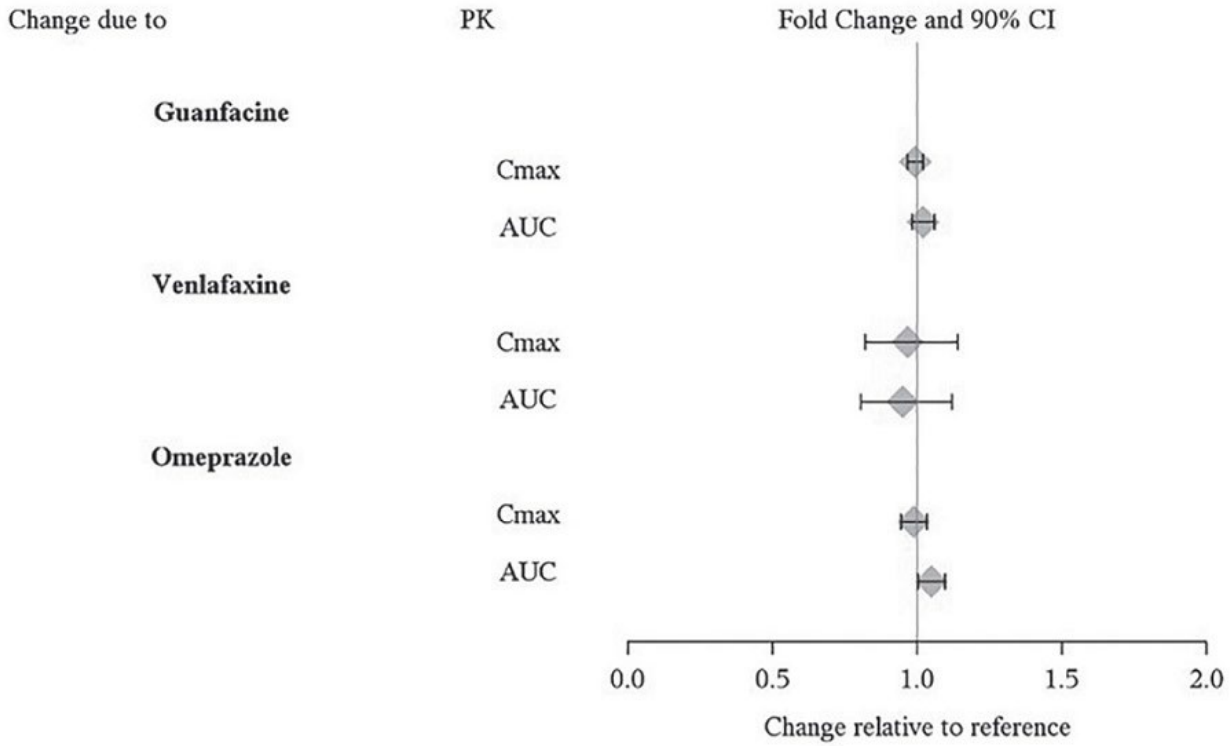
Drug Interaction Studies

Effects of other drugs on the exposures of dextroamphetamine are summarized in Figure 2.

Figure 2. Effect of Other Drugs on Lisdexamfetamine Dimesylate



The effects of lisdexamfetamine dimesylate on the exposures of other drugs are summarized in Figure 3.

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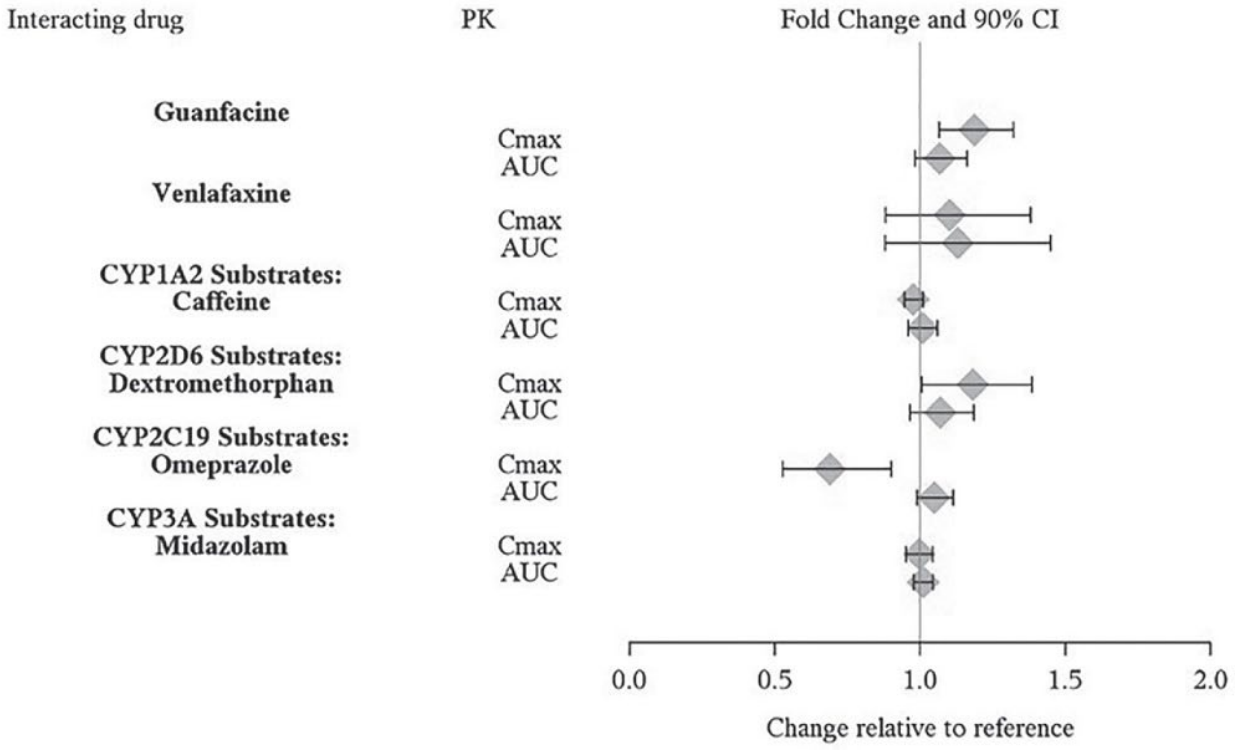
Figure 3. Effect of Lisdexamfetamine Dimesylate on Other Drugs



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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

Carcinogenicity studies of lisdexamfetamine dimesylate have not been performed. 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.

Mutagenesis

Lisdexamfetamine dimesylate was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* and *S. typhimurium* components of the Ames test and in the L5178Y/TK$^{+/-}$ mouse lymphoma assay *in vitro*.

Impairment of Fertility

Amphetamine (d- to l-enantiomer ratio of 3:1) did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day.

13.2 Animal Toxicology and/or Pharmacology

Acute administration of high doses of amphetamine (d- or d, l-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage, in rodents. The significance of these findings to humans is unknown.

14 CLINICAL STUDIES

The efficacy of ARYNTA has been established based on adequate and well-controlled studies of oral lisdexamfetamine dimesylate in the treatment of adults and pediatric patients 6 years and older with ADHD and adults with moderate to severe binge eating disorder (BED). The information below describes the results of the adequate and well-controlled studies of oral lisdexamfetamine dimesylate in patients with ADHD and BED.

14.1 Attention Deficit Hyperactivity Disorder (ADHD)

Pediatric Patients Ages 6 to 12 Years with ADHD

A double-blind, randomized, placebo-controlled, parallel-group study (Study 1) was conducted in pediatric patients ages 6 to 12 years (N=290) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Patients were randomized to receive final doses of 30 mg, 50 mg, or 70 mg of lisdexamfetamine dimesylate or placebo once daily in the morning for a total of four weeks of treatment. All patients receiving lisdexamfetamine dimesylate were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on

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the ADHD Rating Scale (ADHD-RS), an 18-item questionnaire with a score range of 0-54 points that measures the core symptoms of ADHD which includes both hyperactive/impulsive and inattentive subscales. Endpoint was defined as the last post-randomization treatment week (i.e., Weeks 1 through 4) for which a valid score was obtained. All lisdexamfetamine dimesylate dose groups were superior to placebo in the primary efficacy outcome. Mean effects at all doses were similar; however, the highest dose (70 mg/day) was numerically superior to both lower doses (Study 1 in Table 6). The effects were maintained throughout the day based on parent ratings (Conners' Parent Rating Scale) in the morning (approximately 10 am), afternoon (approximately 2 pm), and early evening (approximately 6 pm).

A double-blind, placebo-controlled, randomized, crossover design, analog classroom study (Study 2) was conducted in pediatric patients ages 6 to 12 years (N=52) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Following a 3-week open-label dose optimization with Adderall XR®, patients were randomly assigned to continue their optimized dose of Adderall XR (10 mg, 20 mg, or 30 mg), lisdexamfetamine dimesylate (30 mg, 50 mg, or 70 mg), or placebo once daily in the morning for 1 week each treatment. Efficacy assessments were conducted at 1, 2, 3, 4.5, 6, 8, 10, and 12 hours post-dose using the Swanson, Kotkin, Agler, M.Flynn, and Pelham Deportment scores (SKAMP-DS), a 4-item subscale of the SKAMP with scores ranging from 0 to 24 points that measures deportment problems leading to classroom disruptions. A significant difference in patient behavior, based upon the average of investigator ratings on the SKAMP-DS across the 8 assessments were observed between patients when they received lisdexamfetamine dimesylate compared to patients when they received placebo (Study 2 in Table 6). The drug effect reached statistical significance from hours 2 to 12 post-dose, but was not significant at 1 hour.

A second double-blind, placebo-controlled, randomized, crossover design, analog classroom study (Study 3) was conducted in pediatric patients ages 6 to 12 years (N=129) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Following a 4-week open-label dose optimization with lisdexamfetamine dimesylate (30 mg, 50 mg, 70 mg), patients were randomly assigned to continue their optimized dose of lisdexamfetamine dimesylate or placebo once daily in the morning for 1 week each treatment. A significant difference in patient behavior, based upon the average of investigator ratings on the SKAMP-Deportment scores across all 7 assessments conducted at 1.5, 2.5, 5.0, 7.5, 10.0, 12.0, and 13.0 hours post-dose, were observed between patients when they received lisdexamfetamine dimesylate compared to patients when they received placebo (Study 3 in Table 6, Figure 4).

Pediatric Patients Ages 13 to 17 Years with ADHD

A double-blind, randomized, placebo-controlled, parallel-group study (Study 4) was conducted in pediatric patients ages 13 to 17 years (N=314) who met DSM-IV criteria for ADHD. In this study, patients were randomized in a 1:1:1:1 ratio to a daily morning dose of lisdexamfetamine dimesylate (30 mg/day, 50 mg/day or 70 mg/day) or placebo for a total of four weeks of treatment. All patients receiving lisdexamfetamine dimesylate were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on the ADHD Rating Scale (ADHD-RS). Endpoint was defined as the last post-randomization treatment week (i.e., Weeks 1 through 4) for

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which a valid score was obtained. All lisdexamfetamine dimesylate dose groups were superior to placebo in the primary efficacy outcome (Study 4 in Table 6).

Pediatric Patients Ages 6 to 17 Years: Short-Term Treatment in ADHD

A double-blind, randomized, placebo- and active-controlled parallel-group, dose optimization study (Study 5) was conducted in pediatric patients ages 6 to 17 years (n=336) who met DSM-IV criteria for ADHD. In this eight-week study, patients were randomized to a daily morning dose of lisdexamfetamine dimesylate (30, 50 or 70 mg/day), an active control, or placebo (1:1:1). The study consisted of a Screening and Washout Period (up to 42 days), a 7-week Double-blind Evaluation Period (consisting of a 4-week Dose-Optimization Period followed by a 3-week Dose-Maintenance Period), and a 1-week Washout and Follow-up Period. During the Dose Optimization Period, subjects were titrated until an optimal dose, based on tolerability and investigator's judgment, was reached. lisdexamfetamine dimesylate showed significantly greater efficacy than placebo. The placebo adjusted mean reduction from baseline in the ADHD-RS-IV total score was 18.6. Subjects on lisdexamfetamine dimesylate also showed greater improvement on the Clinical Global Impression-Improvement (CGI-I) rating scale compared to subjects on placebo (Study 5 in Table 6).

Pediatric Patients Ages 6 to 17 Years: Maintenance Treatment in ADHD

Maintenance of Efficacy Study (Study 6) – A double-blind, placebo-controlled, randomized withdrawal study was conducted in pediatric patients ages 6 to 17 years (N=276) who met the diagnosis of ADHD (DSM-IV criteria). A total of 276 patients were enrolled into the study, 236 patients participated in Study 5 and 40 subjects directly enrolled. Subjects were treated with open-label lisdexamfetamine dimesylate for at least 26 weeks prior to being assessed for entry into the randomized withdrawal period. Eligible patients had to demonstrate treatment response as defined by CGI-S <3 and Total Score on the ADHDRS ≤22. Patients that maintained treatment response for 2 weeks at the end of the open label treatment period were eligible to be randomized to ongoing treatment with the same dose of lisdexamfetamine dimesylate (N=78) or switched to placebo (N=79) during the double-blind phase. Patients were observed for relapse (treatment failure) during the 6-week double blind phase. A significantly lower proportion of treatment failures occurred among lisdexamfetamine dimesylate subjects (15.8%) compared to placebo (67.5%) at endpoint of the randomized withdrawal period. The endpoint measurement was defined as the last post randomization treatment week at which a valid ADHD-RS Total Score and CGI-S were observed. Treatment failure was defined as a ≥50% increase (worsening) in the ADHDRS Total Score and a ≥2-point increase in the CGI-S score compared to scores at entry into the double-blind randomized withdrawal phase. Subjects who withdrew from the randomized withdrawal period and who did not provide efficacy data at their last on-treatment visit were classified as treatment failures (Study 6, Figure 5).

Adults: Short-Term Treatment in ADHD

A double-blind, randomized, placebo-controlled, parallel-group study (Study 7) was conducted in adults ages 18 to 55 (N=420) who met DSM-IV criteria for ADHD. In this study, patients were randomized to receive final doses of 30 mg, 50 mg, or 70 mg of lisdexamfetamine dimesylate or placebo for a total of four weeks of treatment. All patients receiving lisdexamfetamine dimesylate were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on

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the ADHD Rating Scale (ADHD-RS). Endpoint was defined as the last post-randomization treatment week (i.e., Weeks 1 through 4) for which a valid score was obtained. All lisdexamfetamine dimesylate dose groups were superior to placebo in the primary efficacy outcome (Study 7 in Table 6).

The second study was a multi-center, randomized, double-blind, placebo-controlled, cross-over, modified analog classroom study (Study 8) of lisdexamfetamine dimesylate to simulate a workplace environment in 142 adults ages 18 to 55 who met DSM-IV-TR criteria for ADHD. There was a 4-week open-label, dose optimization phase with lisdexamfetamine dimesylate (30 mg/day, 50 mg/day, or 70 mg/day in the morning). Patients were then randomized to one of two treatment sequences: 1) lisdexamfetamine dimesylate (optimized dose) followed by placebo, each for one week, or 2) placebo followed by lisdexamfetamine dimesylate, each for one week. Efficacy assessments occurred at the end of each week, using the Permanent Product Measure of Performance (PERMP), a skill-adjusted math test that measures attention in ADHD. PERMP total score results from the sum of the number of math problems attempted plus the number of math problems answered correctly. lisdexamfetamine dimesylate treatment, compared to placebo, resulted in a statistically significant improvement in attention across all post dose time points, as measured by average PERMP total scores over the course of one assessment day, as well as at each time point measured. The PERMP assessments were administered at pre-dose (-0.5 hours) and at 2, 4, 8, 10, 12, and 14 hours post-dose (Study 8 in Table 6, Figure 6).

Adults: Maintenance Treatment in ADHD

A double-blind, placebo-controlled, randomized withdrawal design study (Study 9) was conducted in adults ages 18 to 55 (N=123) who had a documented diagnosis of ADHD or met DSM-IV criteria for ADHD. At study entry, patients must have had documentation of treatment with lisdexamfetamine dimesylate for a minimum of 6 months and had to demonstrate treatment response as defined by Clinical Global Impression Severity (CGI-S) ≤3 and Total Score on the ADHD-RS <22. ADHD-RS Total Score is a measure of core symptoms of ADHD. The CGI-S score assesses the clinician's impression of the patient's current illness state and ranges from 1 (not at all ill) to 7 (extremely ill). Patients that maintained treatment response at Week 3 of the open label treatment phase (N=116) were eligible to be randomized to ongoing treatment with the same dose of lisdexamfetamine dimesylate (N=56) or switched to placebo (N=60) during the double-blind phase. Patients were observed for relapse (treatment failure) during the 6-week double-blind phase. The efficacy endpoint was the proportion of patients with treatment failure during the double-blind phase.

Treatment failure was defined as a ≥50% increase (worsening) in the ADHD-RS Total Score and ≥2-point increase in the CGI-S score compared to scores at entry into the double-blind phase. Maintenance of efficacy for patients treated with lisdexamfetamine dimesylate was demonstrated by the significantly lower proportion of patients with treatment failure (9%) compared to patients receiving placebo (75%) at endpoint during the double-blind phase (Study 9, Figure 7).

Table 6. Summary of Primary Efficacy Results from Short-term Studies of Lisdexamfetamine dimesylate in Pediatric Patients (Ages 6 to 17) and Adults with ADHD

Study Number	Primary Endpoint	Treatment Group	Mean Baseline	LS Mean Change	Placebo-subtracted

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(Age range)			Score (SD)	from Baseline (SE)	Difference (95% CI)
Study 1 (6 – 12 years)	ADHD-RS-IV	Lisdexamfetamine dimesylate (30 mg/day)†	43.2 (6.7)	-21.8 (1.6)	-15.6 (-19.9, -11.2)
		Lisdexamfetamine dimesylate (50 mg/day)†	43.3 (6.7)	-23.4 (1.6)	-17.2 (-21.5, -12.9)
		Lisdexamfetamine dimesylate (70 mg/day)†	45.1(6.8)	-26.7 (1.5)	-20.5 (-24.8, -16.2)
		Placebo	42.4 (7.1)	-6.2 (1.6)	--
Study 2 (6 – 12 years)	Average SKAMP-DS	Lisdexamfetamine dimesylate (30, 50 or 70 mg/day)†	-- ‡	0.8 (0.1)§	-0.9 (-1.1, -0.7)
		Placebo	-- ‡	1.7 (0.1)§	--
Study 3 (6 – 12 years)	Average SKAMP-DS	Lisdexamfetamine dimesylate (30, 50 or 70 mg/day)†	0.9 (1.0)¶	0.7 (0.1)	-0.7 (-0.9, -0.6)
		Placebo	0.7 (0.9)¶	1.4 (0.1)	--
Study 4 (13 – 17 years)	ADHD-RSIV	Lisdexamfetamine dimesylate (30 mg/day)†	38.3 (6.7)	-18.3 (1.2)	-5.5 (-9.0, -2.0)
		Lisdexamfetamine dimesylate (50 mg/day)†	37.3 (6.3)	-21.1 (1.3)	-8.3 (-11.8, -4.8)
		Lisdexamfetamine dimesylate (70 mg/day)†	37.0 (7.3)	-20.7 (1.3)	-7.9 (-11.4, -4.5)
		Placebo	38.5 (7.1)	-12.8 (1.2)	--
Study 5 (6 – 17 years)	ADHD-RS-IV	Lisdexamfetamine dimesylate (30, 50 or 70 mg/day)†	40.7 (7.3)	-24.3 (1.2)	-18.6 (-21.5, -15.7)
		Placebo	41.0 (7.1)	-5.7 (1.1)	--
Study 7 (18 – 55 years)	ADHD-RS-IV	Lisdexamfetamine dimesylate (30 mg/day)†	40.5 (6.2)	-16.2 (1.1)	-8.0 (-11.5, -4.6)
		Lisdexamfetamine dimesylate (50 mg/day)†	40.8 (7.3)	-17.4 (1.0)	-9.2 (-12.6, -5.7)
		Lisdexamfetamine dimesylate (70 mg/day)†	41.0 (6.0)	-18.6 (1.0)	-10.4 (-13.9, -6.9)
		Placebo	39.4 (6.4)	-8.2 (1.4)	--

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Study 8 (18 – 55 years)	Average PERMP	Lisdexamfetamine dimesylate (30, 50 or 70 mg/day)†	260.1 (86.2)¶	312.9 (8.6)§	23.4 (15.6, 31.2)
		Placebo	261.4 (75.0)¶	289.5 (8.6)§	--

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

* Difference (drug minus placebo) in least-squares mean change from baseline.

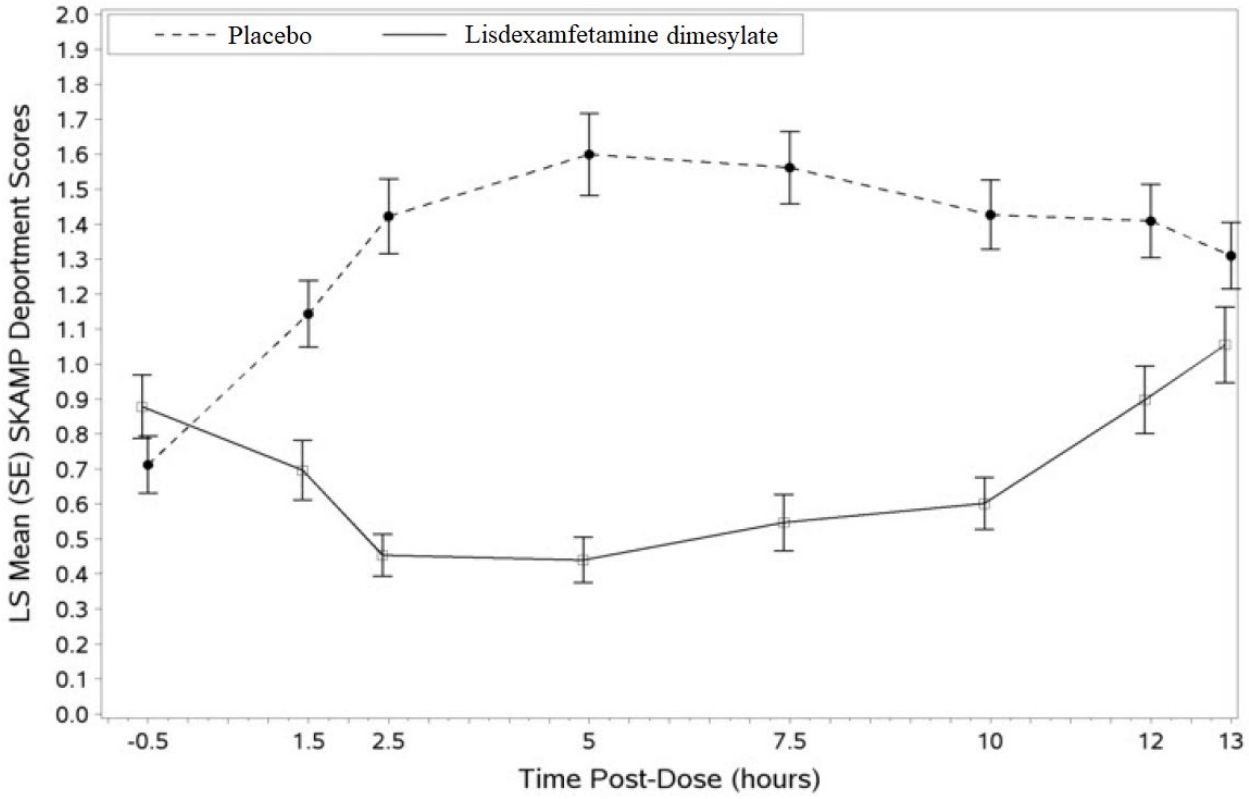
† Doses statistically significantly superior to placebo.

‡ Pre-dose SKAMP-DS was not collected.

§ LS Mean for SKAMP-DS (Study 2 and 3) or PERMP (Study 8) is post-dose average score over all sessions of the treatment day, rather than change from baseline.

¶ Pre-dose SKAMP-DS (Study 3) or PERMP (Study 8) total score, averaged over both periods.

Figure 4. LS Mean SKAMP Deportment Subscale Score by Treatment and Time-point for Pediatric Patients Ages 6 to 12 with ADHD after 1 Week of Double-Blind Treatment (Study 3)



Higher score on the SKAMP-Deportment scale indicates more severe symptoms.

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Figure 5. Kaplan-Meier Estimated Proportion of Patients with Treatment Failure for Pediatric Patients Ages 6 to 17 (Study 6)

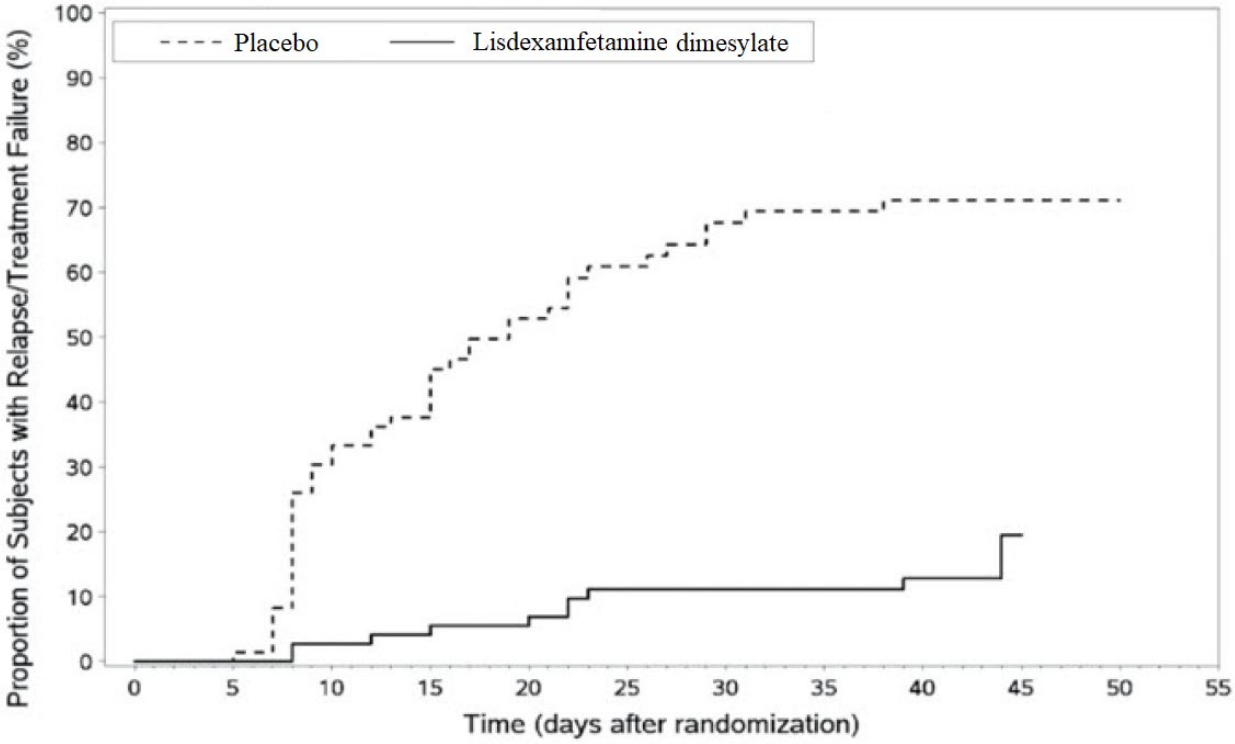

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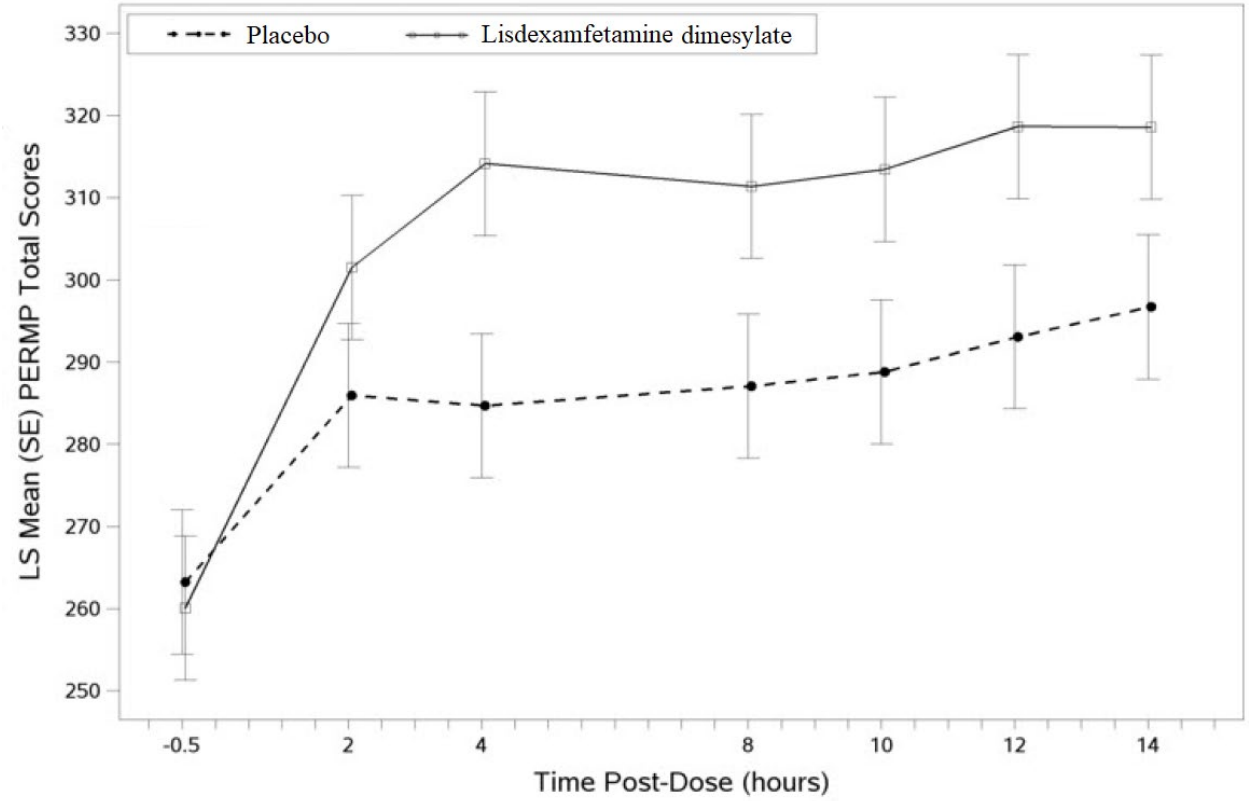
Figure 6. LS Mean (SE) PERMP Total Score by Treatment and Time-point for Adults Ages 18 to 55 with ADHD after 1 Week of Double-Blind Treatment (Study 8)



Higher score on the PERMP scale indicates less severe symptoms.

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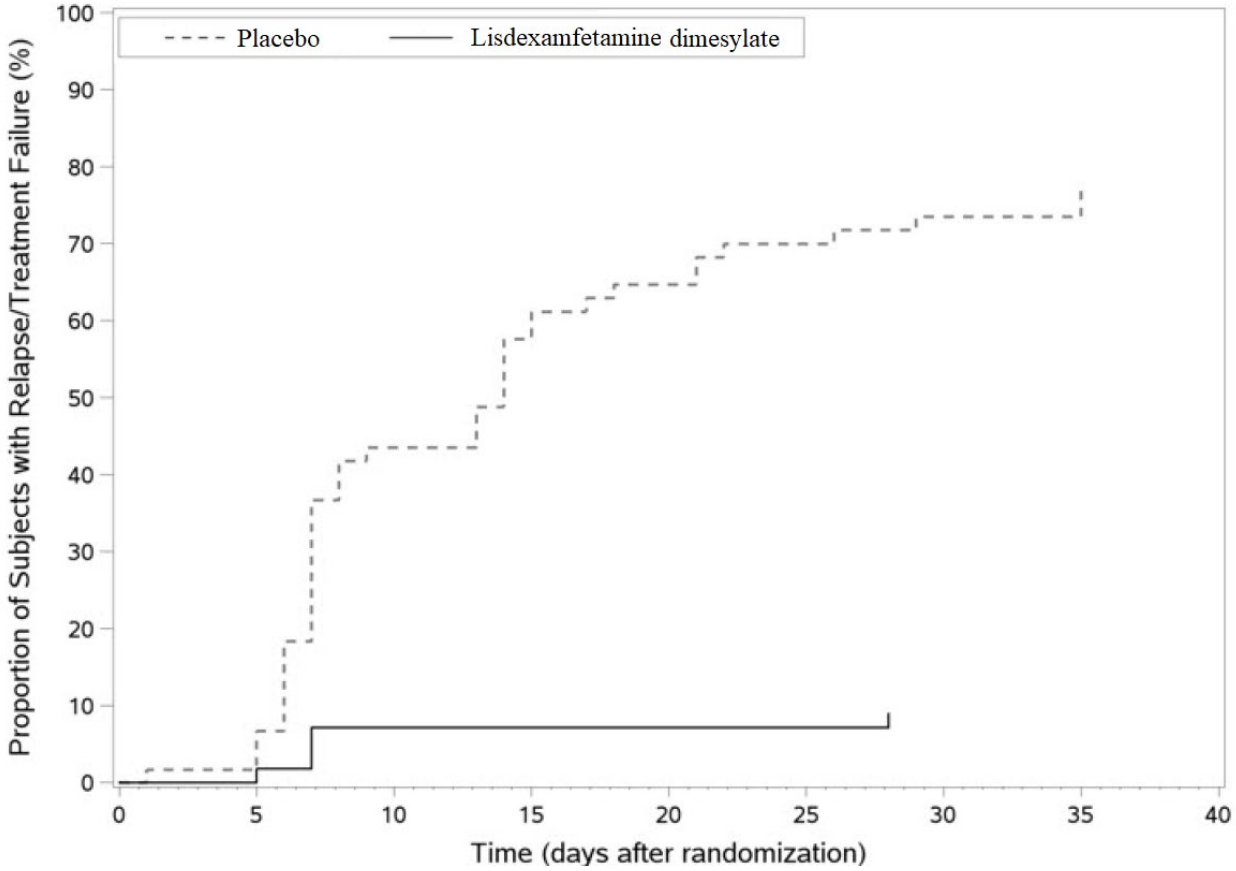
Figure 7. Kaplan-Meier Estimated Proportion of Subjects with Relapse in Adults with ADHD (Study 9)



14.2 Binge Eating Disorder (BED)

A phase 2 study evaluated the efficacy of lisdexamfetamine dimesylate 30, 50 and 70 mg/day compared to placebo in reducing the number of binge days/week in adults with at least moderate to severe BED. This randomized, double-blind, parallel-group, placebo-controlled, forced-dose titration study (Study 10) consisted of an 11-week double-blind treatment period (3 weeks of forced-dose titration followed by 8 weeks of dose maintenance). Lisdexamfetamine dimesylate 30 mg/day was not statistically different from placebo on the primary endpoint. The 50 and 70 mg/day doses were statistically superior to placebo on the primary endpoint.

The efficacy of lisdexamfetamine dimesylate in the treatment of BED was demonstrated in two 12-week randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose-optimization studies (Study 11 and Study 12) in adults aged 18-55 years (Study 11: N=374, Study 12: N=350) with moderate to severe BED. A diagnosis of BED was confirmed using DSM-IV criteria for BED. Severity of BED was determined based on having at least 3 binge days per week for 2 weeks prior to the baseline visit and on having a Clinical Global Impression Severity (CGI-S) score of ≥4 at the baseline visit. For both studies, a binge day was defined as a day with at least 1 binge episode, as determined from the subject's daily binge diary.

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Both 12-week studies consisted of a 4-week dose-optimization period and an 8-week dose-maintenance period. During dose-optimization, subjects assigned to lisdexamfetamine dimesylate began treatment at the titration dose of 30 mg/day and, after 1 week of treatment, were subsequently titrated to 50 mg/day. Additional increases to 70 mg/day were made as tolerated and clinically indicated. Following the dose-optimization period, subjects continued on their optimized dose for the duration of the dose-maintenance period.

The primary efficacy outcome for the two studies was defined as the change from baseline at Week 12 in the number of binge days per week. Baseline is defined as the weekly average of the number of binge days per week for the 14 days prior to the baseline visit. Subjects from both studies on lisdexamfetamine dimesylate had a statistically significantly greater reduction from baseline in mean number of binge days per week at Week 12. In addition, subjects on lisdexamfetamine dimesylate showed greater improvement as compared to placebo across key secondary outcomes with higher proportion of subjects rated improved on the CGI-I rating scale, higher proportion of subjects with 4-week binge cessation, and greater reduction in the Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) total score.

Table 7. Summary of Primary Efficacy Results in BED

Study Number	Treatment Group	Primary Efficacy Measure: Binge Days per Week at Week 12		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)
Study 11	Lisdexamfetamine dimesylate (50 mg or 70 mg/day)†	4.79 (1.27)	-3.87 (0.12)	-1.35 (-1.70, -1.01)
	Placebo	4.60 (1.21)	-2.51 (0.13)	--
Study 12	Lisdexamfetamine dimesylate (50 mg or 70 mg/day)†	4.66 (1.27)	-3.92 (0.14)	-1.66 (-2.04, -1.28)
	Placebo	4.82 (1.42)	-2.26 (0.14)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
* Difference (drug minus placebo) in least-squares mean change from baseline.
† Doses statistically significantly superior to placebo.

A double-blind, placebo controlled, randomized withdrawal design study (Study 13) was conducted to evaluate maintenance of efficacy based on time to relapse between lisdexamfetamine dimesylate and placebo in adults aged 18 to 55 (N=267) with moderate to severe BED. In this longer-term study patients who had responded to lisdexamfetamine dimesylate in the preceding 12-week open-label treatment phase were randomized to continuation of lisdexamfetamine dimesylate or placebo for up to 26 weeks of observation for relapse. Response in the open-label phase was defined as 1 or fewer binge days each week for four consecutive weeks prior to the last visit at the end of the 12-week open-label phase and a CGI-S score of 2 or less at the same visit. Relapse during the double-blind phase was defined as having 2 or more binge days each week for two consecutive weeks (14 days) prior to any visit and having an increase in CGI-S score of 2 or more points compared to the randomized-withdrawal baseline. Maintenance of efficacy for

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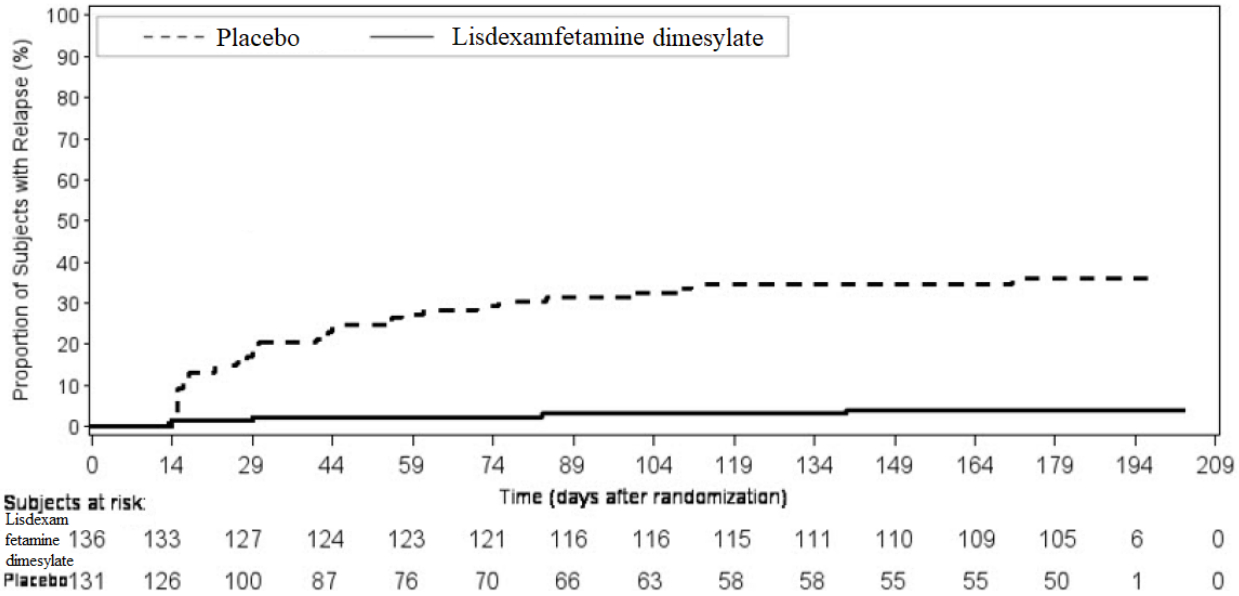
patients who had an initial response during the open-label period and then continued on lisdexamfetamine dimesylate during the 26-week double-blind randomized-withdrawal phase was demonstrated with lisdexamfetamine dimesylate being superior over placebo as measured by time to relapse.

Figure 8. Kaplan-Meier Estimated Proportions of Subjects with Relapse in Adults with BED (Study 13)



Examination of population subgroups based on age (there were no patients over 65), gender, and race did not reveal any clear evidence of differential responsiveness in the treatment of BED.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ARYNTA oral solution is a clear colorless solution contains 10 mg/mL of lisdexamfetamine dimesylate. It is packaged in 100 mL PET bottles with a child resistant closure as follows:

Each sealed bottle is co-packaged with one press-in bottle adapter and one oral dosing syringe.

NDC Number	Size
24338-019-01	100 mL

16.2 Storage and Handling

ARYNTA is stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Keep the container tightly closed. Throw away (discard) any remaining ARYNTA 30 days after first opening the bottle.

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17 PATIENT COUNSELING INFORMATION

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

Abuse, Misuse, and Addiction

Educate patients and their families about the risks of abuse, misuse, and addiction of ARYNTA, which can lead to overdose and death, and proper disposal of any unused drug *[see Warnings And Precautions (5.1), Drug Abuse and Dependence (9.2), Overdosage (10)]*. Advise patients to store ARYNTA in a safe place, preferably locked, and instruct patients to not give ARYNTA to anyone else.

Risks to Patients with Serious Cardiac Disease

Advise patients that there are potential risks to patients with serious cardiac disease, including sudden death, with ARYNTA use. Instruct patients to contact a healthcare provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease *[see Warnings and Precautions (5.2)]*.

Increased Blood Pressure and Heart Rate

Instruct patients that ARYNTA can cause elevations of their blood pressure and pulse rate and they should be monitored for such effects.

Psychiatric Adverse Reactions

Advise patients that ARYNTA at recommended doses may cause psychotic or manic symptoms even in patients without prior history of psychotic symptoms or mania *[see Warnings and Precautions (5.4)]*.

Long-Term Suppression of Growth in Pediatric Patients

Advise patients that ARYNTA may cause slowing of growth including weight loss *[see Warnings and Precautions (5.5)].*

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

Instruct patients beginning treatment with ARYNTA about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change from pale, to blue, to red. Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes. Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking ARYNTA. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients *[see Warnings and Precautions (5.6)]*.

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome with concomitant use of ARYNTA and other serotonergic drugs including SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort, and with drugs that impair metabolism of serotonin (in particular MAOIs, both those intended to treat psychiatric disorders and also others

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such as Linezolid *[see Contraindications (4), Warnings and Precautions (5.7) and Drug Interactions (7.1)]*. Advise patients to contact their healthcare provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome.

Concomitant Medications

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

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

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

Pregnancy Registry

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

Pregnancy

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

Lactation

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

Manufactured for:
Azurity Pharmaceuticals, Inc.
Woburn, MA 01801

This products labeling may have been updated. For current Full Prescribing Information, please visit www.arynta.com

PN: #####-#####

Rev: 03; 6/2025

Reference ID: 5609173

MEDICATION GUIDE
ARYNTA™ (AH-RIN-TAH)
(lisdexamfetamine dimesylate)
Oral Solution, CII

What is the most important information I should know about ARYNTA?

ARYNTA may cause serious side effects, including:

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

  Your healthcare provider should check you or your child carefully for heart problems before starting treatment with ARYNTA. Tell your healthcare provider if you or your child have any heart problems, heart disease, or heart defects.

  Call your healthcare provider right away or go to the nearest hospital emergency room right away if you or your child have any signs of heart problems such as chest pain, shortness of breath, or fainting during treatment with ARYNTA.
- **Increased blood pressure and heart rate.**
  - Your healthcare provider should check you or your child's blood pressure and heart rate regularly during treatment with ARYNTA.
- **Mental (psychiatric) problems, including:**
  - new or worse behavior and thought problems
  - new or worse bipolar illness
  - new psychotic symptoms (such as hearing voices, or seeing or believing things that are not real) or new manic symptoms

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

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

What is ARYNTA?

ARYNTA is a central nervous system (CNS) stimulant prescription medicine used for the treatment of:

- Attention Deficit Hyperactivity Disorder (ADHD) in adults and children 6 years of age and older. ARYNTA may help increase attention and decrease impulsiveness and hyperactivity in people with ADHD.
- Moderate to severe binge eating disorder (BED) in adults. ARYNTA may help reduce the number of binge eating days in people with BED.

ARYNTA is not for use in children under 6 years of age with ADHD.

ARYNTA is not for weight loss. It is not known if ARYNTA is safe and effective for the treatment of obesity.

It is not known if ARYNTA is safe and effective for use in children with BED.

ARYNTA is a federally controlled substance (CII) because it contains lisdexamfetamine dimesylate that can be a target for people who abuse prescription medicines or street drugs. Keep ARYNTA in a safe place to protect it from theft. Never give your ARYNTA to anyone else because it may cause death or harm them. Selling or giving away ARYNTA may harm others and is against the law.

Do not take ARYNTA if you or your child are:

- allergic to amphetamine products or any of the ingredients in ARYNTA. See the end of this Medication Guide for a complete list of ingredients in ARYNTA.
- taking, or have stopped taking in the last 14 days, a medicine called a Monoamine Oxidase Inhibitor (MAOI).
- being treated with the antibiotic linezolid or intravenous methylene blue.

Before taking ARYNTA, tell your healthcare provider about all medical conditions, including if you or your child:

- have heart problems, heart disease, heart defects, or high blood pressure, or have a family history of sudden death or heart rhythm problems
- have mental problems including psychosis, mania, bipolar illness, or depression or have a family history of suicide, bipolar illness, or depression
- have circulation problems in fingers and toes
- have kidney problems
- have or had repeated movements or sounds (tics) or Tourette's syndrome, or have a family history of tics or Tourette's syndrome
- are pregnant or plan to become pregnant. ARYNTA may harm the unborn baby. Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with ARYNTA.
  - There is a pregnancy registry for women who are exposed to ARYNTA during pregnancy. If you become pregnant during treatment with ARYNTA, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visiting online at https://womensmentalhealth.org/clinical-and researchprograms/pregnancyregistry/adhdmedications/.
- are breastfeeding or plan to breastfeed. ARYNTA passes into breast milk. You should not breastfeed during treatment with ARYNTA. Talk to your healthcare provider about the best way to feed the baby during treatment with ARYNTA.

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

ARYNTA can affect the way other medicines work and other medicines may affect how ARYNTA works. Taking ARYNTA with other medicines can cause serious side effects. Sometimes the doses of other medicines will need to be changed during treatment with ARYNTA.

Especially tell your healthcare provider if you or your child take:

- selective serotonin reuptake inhibitors (SSRIs)
- medicines used to treat migraine headaches called triptans
- lithium
- tramadol
- buspirone
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants
- fentanyl
- tryptophan
- St. John's Wort

Keep a list of all medicines to show your healthcare provider and pharmacist when you get a new medicine.
Your healthcare provider will decide if ARYNTA can be taken with other medicines.

Do not start any new medicine during treatment with ARYNTA without talking to your healthcare provider first.

How should ARYNTA be taken?

- Read the Instructions for Use for detailed instructions about how to measure and take a dose of ARYNTA.
- Take ARYNTA exactly as prescribed by your or your child's healthcare provider.
- Your healthcare provider may change the dose if needed.
- Take ARYNTA 1 time each day in the morning with or without food.
- Taking ARYNTA in the afternoon may cause trouble sleeping.
- If you or your child take too much ARYNTA, call your healthcare provider or Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of ARYNTA?

ARYNTA may cause serious side effects, including:

- See **"What is the most important information I should know about** ARYNTA**?"**
- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with ARYNTA. ARYNTA treatment may be stopped if your child is not growing or gaining weight as expected.
- **Circulation problems in fingers and toes (Peripheral vasculopathy, including Raynaud's phenomenon).** Signs and symptoms may include:
  - fingers or toes may feel numb, cool, painful
  - fingers or toes may change color from pale, to blue, to red

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

  Call your healthcare provider right away if you or your child have any signs of unexplained wounds appearing on fingers or toes during treatment with ARYNTA.
- **Serotonin syndrome.** A potentially life-threatening problem called serotonin syndrome may happen when ARYNTA is taken with certain other medicines. Stop taking ARYNTA and call your healthcare provider or go to the nearest hospital emergency room right away if you or your child develop any of the following signs and symptoms of serotonin syndrome:
  - agitation
  - flushing
  - coma
  - loss of coordination
  - dizziness
  - seeing or hearing things that are not real (hallucination)
  - high body temperature (hyperthermia)
  - fast heartbeat
  - seizures
  - sweating
  - confusion
  - tremors, stiff muscles, or muscle twitching
  - changes in blood pressure
  - nausea, vomiting, diarrhea
- **New or worsening tics or worsening Tourette's syndrome.** Tell your healthcare provider if you or your child get any new or worsening tics or worsening Tourette's syndrome during treatment with ARYNTA.

The most common side effects of ARYNTA in children 6 to 17 years old and adults with ADHD include:

- loss of appetite (anorexia)
- decreased appetite
- diarrhea
- dry mouth
- trouble sleeping
- stomach pain
- anxiety
- weight loss
- dizziness
- irritability
- nausea
- vomiting

The most common side effects of ARYNTA in adults with BED include:

- dry mouth
- decreased appetite
- constipation
- anxiety
- trouble sleeping
- increased heart rate
- feeling jittery

These are not all the possible side effects of ARYNTA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ARYNTA**?**

- Store ARYNTA at room temperature between 68°F to 77°F (20°C to 25°C).
- Store ARYNTA in a safe place (like a locked cabinet).
- Keep the container tightly closed.
- Throw away (discard) any remaining ARYNTA 30 days after first opening the bottle.
- Dispose of remaining, unused, or expired ARYNTA by a medicine take-back program at a U.S. Drug Enforcement Administration (DEA) authorized collection site. If no take-back program or DEA authorized collector is available, mix ARYNTA with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the solution in a container such as a sealed plastic bag and throw away ARYNTA in the household trash. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Keep ARYNTA and all medicines out of the reach of children.

General information about the safe and effective use of ARYNTA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ARYNTA for a condition for which it was not prescribed. Do not give ARYNTA to other people, even if they have the same symptoms that you have. It may harm them and it is against the law. You can ask your pharmacist or healthcare provider for information about ARYNTA that is written for healthcare professionals.

What are the ingredients in ARYNTA?

Active ingredient: lisdexamfetamine dimesylate

Inactive ingredients: dibasic sodium phosphate dihydrate, methylparaben sodium, monobasic sodium phosphate dihydrate, propylparaben sodium, propylene glycol, saccharin sodium, hydrochloric acid, sodium hydroxide and purified water.

Manufactured for:
Azurity Pharmaceuticals, Inc.
Woburn, MA 01801

This products labeling may have been updated. For current Full Prescribing Information, please visit www.arynta.com

PN: #####-#####

Rev: 03; 6/2025

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 6/2025

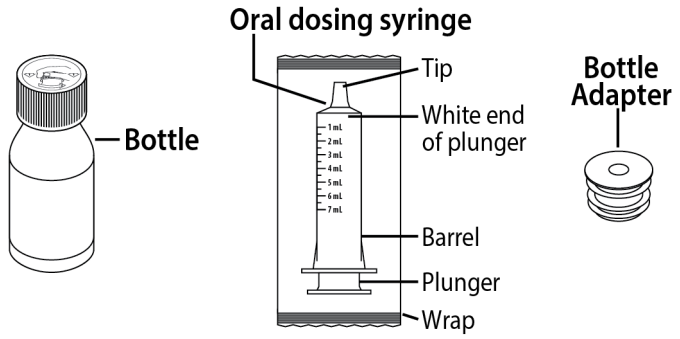
INSTRUCTIONS FOR USE

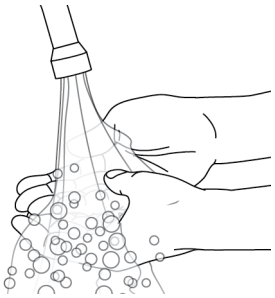
ARYNTA™ (AH-RIN-TAH)
(lisdexamfetamine dimesylate)
oral solution, CII

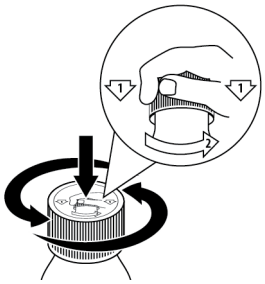
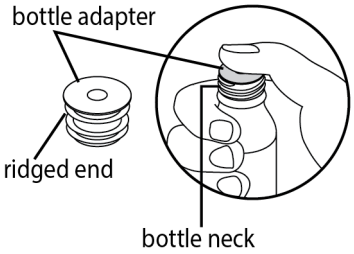
This Instructions for Use contains information on how to measure and take a dose of ARYNTA.

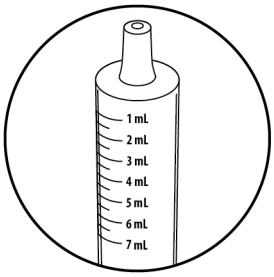
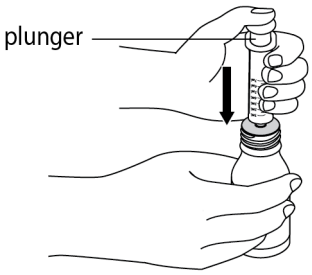
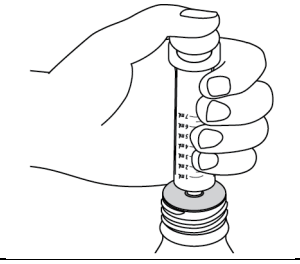
Important Information You Need to Know Before Taking ARYNTA:

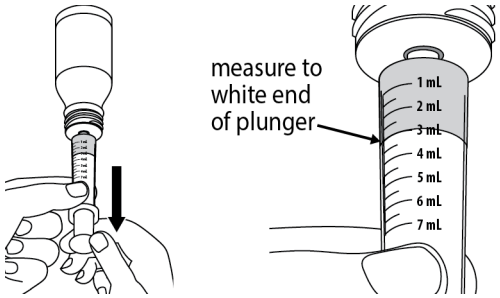
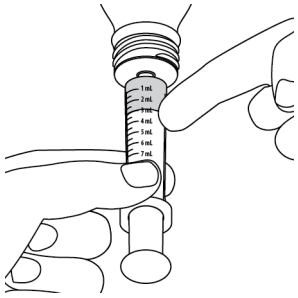
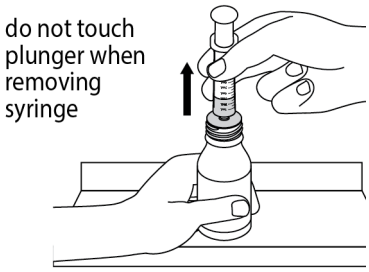
- ARYNTA is for oral use only (taken by mouth).
- Take ARYNTA with or without food.
- Use the oral dosing syringe and bottle adapter that come with ARYNTA to measure and take a dose of ARYNTA.
- Check the expiration date (EXP) on the carton label. **Do not** take ARYNTA after the expiration date has passed. Call your healthcare provider or pharmacist if your medicine is expired.
- Record the date you first opened the bottle on the space provided on the bottle. Throw away (discard) any remaining ARYNTA 30 days after first opening the bottle. See **"Disposing of ARYNTA"** below.

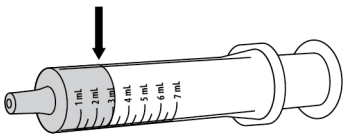
Supplies included in the ARYNTA carton (See Figure A): • 1 bottle of ARYNTA • 1 oral dosing syringe • 1 bottle adapter • 1 Prescribing Information with Medication Guide • 1 Instructions for Use	Figure A 

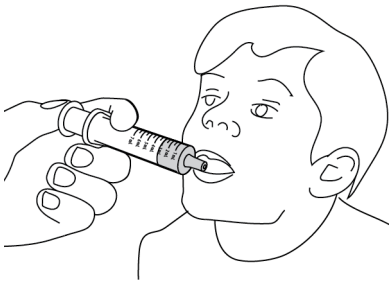
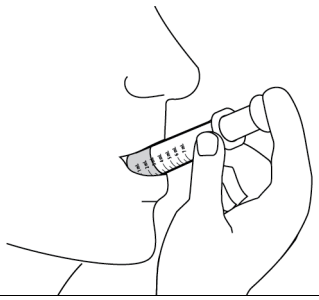
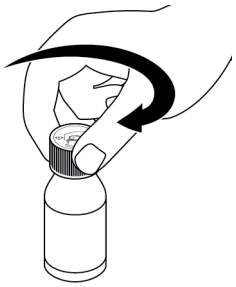
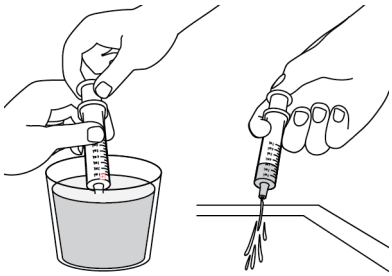
Step 1: **Preparing to take ARYNTA** • Wash and dry your hands (see Figure B). • Remove the tamper evident seal from the carton. • Take the ARYNTA bottle, 1 oral dosing syringe, 1 bottle adapter, 1 Prescribing Information with Medication Guide and 1 Instructions for Use out of the carton. Tell your pharmacist right away if you are missing any supplies from the carton.	Figure B 

Step 2:
• Place the ARYNTA bottle on a flat surface like a table or countertop and remove the child resistant cap by pressing down and turning counterclockwise (see Figure C).
 	
• Insert the bottle adapter (first time use only):
  ○ Hold the bottle firmly and insert the ridged end of the bottle adapter into the neck of the bottle.
  ○ Firmly push the bottle adapter all the way down with your thumb until the top of the adapter is aligned and flat (flush) with the top of the bottle (See Figure D).
• **Do not** remove the bottle adapter after it has been inserted into the bottle.
	Figure C
	 
	Figure D
	 

Step 3: • Tear the plastic wrap and remove the oral dosing syringe from the wrap. • Check the ARYNTA oral dosing syringe to find the right dose in milliliters (mL) that has been prescribed by the healthcare provider (see Figure E). • Make sure the oral dosing syringe is dry.	Figure E 
Step 4: • Insert the tip of the oral dosing syringe with a slight twisting motion into the adapter (see Figure F). • Push the plunger all the way down (see Figure G).	Figure F  Figure G 

Step 5: **Measuring the dose of ARYNTA:** • With the tip of the oral dosing syringe in place in the adapter, hold the ARYNTA bottle with 1 hand and turn the bottle upside down. Pull the plunger down until the white end of the plunger reaches the number of mL you need for the prescribed dose (see Figure H). • Push and pull the plunger a few times to make sure that there are no air bubbles. • Tap the barrel of the oral dosing syringe if needed to get rid of any air bubbles (see Figure I).	Figure H  Figure I 
Step 6: • Turn the bottle over and place it upright on a table or countertop, then remove the oral dosing syringe from the bottle adapter by twisting it out gently (see Figure J).	Figure J 

Step 7:
• Check that the correct dose in mL was pulled up into the oral dosing syringe (see Figure K).
• If the dose is **not** correct:
  ○ Insert the oral syringe tip back into the bottle and fully push in the plunger to the bottom of the syringe barrel so that all the oral solution flows back into the bottle.
  ○ Repeat Steps 4 through 6.
	Figure K
	 

Step 8: **Taking the dose of ARYNTA:** • The person should be in a seated position before taking ARYNTA. • Tilt the head slightly upwards. • Place the oral dosing syringe into the mouth and point it toward the cheek (see Figure L). • Close the mouth tightly around the oral dosing syringe and slowly push the plunger all the way down to give the ARYNTA dose (see Figure M). • After all the medicine has been taken, remove the oral dosing syringe from the mouth.	Figure L  Figure M 
Step 9: **Closing the bottle:** • Put the ARYNTA cap back on the bottle and close the cap tightly by turning the cap clockwise (see Figure N).	Figure N 
Step 10: **Cleaning up:** • Clean the oral dosing syringe after each use by rinsing with tap water (see Figure O). • Allow the oral dosing syringe to dry and keep it in a safe place for the next use. • Wash and dry your hands.	Figure O 

Disposing of ARYNTA:

- Throw away (discard) any remaining ARYNTA 30 days after first opening the bottle.
- Dispose of remaining, unused, or expired ARYNTA by a medicine take-back program at a U.S. Drug Enforcement Administration (DEA) authorized collection site. If no take-back program or DEA authorized collector is available, mix ARYNTA with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the solution in a container such as a sealed plastic bag and throw away ARYNTA in the household trash. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Storing ARYNTA:

- Store ARYNTA at room temperature between 68°F to 77°F (20°C to 25°C).
- Store ARYNTA in a safe place (like a locked cabinet).
- Keep the container tightly closed.

Keep ARYNTA and all medicines out of the reach of children.

Manufactured for:
Azurity Pharmaceuticals, Inc.
Woburn, MA 01801

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