Physician's Prescribing Information

NAME OF THE MEDICINAL PRODUCT

LISDEXA S.K. 10 MG/ML ORAL SOLUTION

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral solution contains 10 mg lisdexamfetamine dimesylate

Excipient(s) with known effect
LISDEXA S.K. 10 MG/ML ORAL SOLUTION contains 1 mg sodium methyl parahydroxybenzoate, 0.1 mg sodium propyl parahydroxybenzoate and 100 mg propylene glycol per ml of oral solution.

For the full list of excipients, see section "DESCRIPTION" below.

PHARMACEUTICAL FORM

Oral solution.
Clear, colorless solution.

WARNING: ABUSE, MISUSE AND ADDICTION
LISDEXA S.K. 10 MG/ML ORAL SOLUTION 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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION., 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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION 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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION 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), and Drug Abuse Dependence (9.2,)]*.

1 INDICATIONS AND USAGE

LISDEXA S.K. 10 MG/ML ORAL SOLUTION is a central nervous system (CNS) stimulant indicated for:

- the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients ages 6 years and above.
- the treatment of Moderate to Severe Binge Eating Disorder (BED) for patients over 18 years.

Limitation of Use:
LISDEXA S.K. 10 MG/ML ORAL SOLUTION 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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION 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 CNS stimulants, including LISDEXA S.K. 10 MG/ML ORAL SOLUTION , 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)]*.

To reduce the abuse of CNS stimulants including LISDEXA S.K. 10 MG/ML ORAL SOLUTION , assess the risk of abuse, prior to prescribing. After prescribing, keep careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and re-evaluate the need for LISDEXA S.K. 10 MG/ML ORAL SOLUTION use *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.)]*.

2.2 General Administration Information

Take LISDEXA S.K. 10 MG/ML ORAL SOLUTION orally in the morning with or without food; avoid afternoon doses because of the potential for insomnia.

- A graduated oral syringe and a Press-In Bottle Adapter (PIBA) are provided with the product.
- For instructions on administration of this medicinal product, see section 15.

2.3 Dosage for Treatment of ADHD

The recommended starting dosage in adults and pediatric patients 6 years and older is 30 mg (equivalent to 3 ml) once daily in the morning. Dosage may be adjusted in increments of 10 mg (equivalent to 1 ml) or 20 mg (equivalent to 2 ml) at approximately weekly intervals up to maximum recommended dosage of 70 mg (equivalent to 7 ml) 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 (equivalent to 3 ml) once daily to be titrated in increments of 20 mg (equivalent to 2 ml) at approximately weekly intervals to

achieve the recommended target dose of 50 to 70 mg (equivalent to 5 ml to 7 ml) once daily. The maximum recommended dosage is 70 mg/once daily (equivalent to 7 ml/once daily) *[see Clinical Studies (14.2)]*. Discontinue LISDEXA S.K. 10 MG/ML ORAL SOLUTION 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 m2), the maximum dosage should not exceed 50 mg (equivalent to 5 ml) once daily. In patients with end stage renal disease (ESRD, GFR < 15 mL/min/1.73 m2), the maximum recommended dosage is 30 mg (equivalent to 3 ml) 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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION dosage accordingly *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Oral solution
Clear, colorless solution.

4 CONTRAINDICATIONS

LISDEXA S.K. 10 MG/ML ORAL SOLUTION is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 11.
  Known hypersensitivity to amphetamine products 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

LISDEXA S.K. 10 MG/ML ORAL SOLUTION has a high potential for abuse and misuse. The use of LISDEXA S.K. 10 MG/ML ORAL SOLUTION exposes individuals to the risks of abuse and misuse ,which can lead to the development of a substance use disorder, including addiction. LISDEXA S.K. 10 MG/ML ORAL SOLUTION 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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION , can result in overdose and death, *[see Overdosage (10)]*,and this risk is increase

with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing LISDEXA S.K. 10 MG/ML ORAL SOLUTION , 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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION in a safe place, preferably locked, and instruct patients to not give LISDEXA S.K. 10 MG/ML ORAL SOLUTION to anyone else. Throughout LISDEXA S.K. 10 MG/ML ORAL SOLUTION treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

Driving and using machines
LISDEXA S.K. 10 MG/ML ORAL SOLUTION can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation and blurred vision. These could have a moderate influence on the ability to drive and use machines. Patients should be warned of these possible effects and advised that if affected, they should avoid potentially hazardous activities such as driving or operating machinery.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per 1 mL of oral solution, that is to say essentially 'sodium-free'.

This medicinal product contains 100 mg propylene glycol in each mL of oral solution.
LISDEXA S.K. 10 MG/ML ORAL SOLUTION contains sodium methyl parahydroxybenzoate and sodium propyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).

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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION 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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION -treated patients for potential tachycardia and hypertension.

5.4 Psychiatric Adverse Reactions
Exacerbation of Pre-existing Psychosis
CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a /manic or mixed episode. Prior to initiating LISDEXA S.K. 10 MG/ML ORAL SOLUTION 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).

New Psychotic or Manic Symptoms

CNS stimulants, at the recommendeddosage, 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-treated patients compared to 0% of placebo-treated patients. If such symptoms occur, consider discontinuing LISDEXA S.K. 10 MG/ML ORAL SOLUTION .

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 Lisdexamfetamine Dimesylate capsules pediatric patients ages 6 to 12 years old with ADHD, there was a dose-related decrease in weight in the Lisdexamfetamine Dimesylate 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 Lisdexamfetamine Dimesylate-treated pediatric patients.

Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted. LISDEXA S.K. 10 MG/ML ORAL SOLUTION 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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION , 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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for Lisdexamfetamine Dimesylate -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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION (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, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

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

Discontinue treatment with Lisdexamfetamine Dimesylate and any concomitant serotonergic agents immediately if symptoms of serotonin syndrome occur and initiate supportive symptomatic treatment. If concomitant use of Lisdexamfetamine Dimesylate with other serotonergic drugs or CYP2D6 inhibitors is clinically warranted, initiate Lisdexamfetamine Dimesylate with lower doses, monitor patients for the emergence of serotonin syndrome during drug initiation or titration, and informpatients 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 Lisdexamfetamine Dimesylate , assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor Lisdexamfetamine Dimesylate - 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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION *[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)]*
- Increase 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.

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 Lisdexamfetamine Dimesylate - 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, 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 Lisdexamfetamine Dimesylate capsules - 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 Lisdexamfetamine Dimesylate capsules-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 Lisdexamfetamine Dimesylate 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 Lisdexamfetamine Dimesylate 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 Lisdexamfetamine Dimesylate.or placebo are presented in Tables 1, 2, and 3 below.

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	23%	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%
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 capsules 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 well 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 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 capsules , 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 capsules -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[1]	20%	8%
Decreased Appetite	8%	2%
Increased Heart Rate[2]	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%

	Lisdexamfetamine Dimesylate (n=373)	Placebo (n=372)
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%

[1] Includes all preferred terms containing the word "insomnia."
[2] 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Amphetamines

Table 5 Drugs having clinically important interactions with amphetamines.

MAO Inhibitors (MAOI)	
Clinical Impact	MAOI antidepressants slow amphetamine metabolism, increasing amphetamines effect on the release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of hypertensive crisis. Toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Intervention	Do not administer LISDEXA S.K. 10 MG/ML ORAL SOLUTION during or within 14 days following the administration of MAOI *[see Contraindications (4)]*.
Serotonergic Drugs	
Clinical Impact	The concomitant use of LISDEXA S.K. 10 MG/ML ORAL SOLUTION and serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome, particularly during LISDEXA S.K. 10 MG/ML ORAL SOLUTION initiation or dosage increase. If serotonin syndrome occurs, discontinue LISDEXA S.K. 10 MG/ML ORAL SOLUTION and the concomitant serotonergic drug(s) *[see Warnings and Precautions (5.7)]*.
CYP2D6 Inhibitors	
Clinical Impact	The concomitant use of LISDEXA S.K. 10 MG/ML ORAL SOLUTION and CYP2D6 inhibitors may increase the exposure of dextroamphetamine, the active metabolite of LISDEXA S.K. 10 MG/ML ORAL SOLUTION compared to the use of the drug alone and increase the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during LISDEXA S.K. 10 MG/ML ORAL SOLUTION initiation and after a dosage increase. If serotonin syndrome occurs, discontinue LISDEXA S.K. 10 MG/ML ORAL SOLUTION and the CYP2D6 inhibitor *[see Warnings and Precautions (5.7) and Overdosage (10)]*.
Alkalinizing Agents	
Clinical Impact	Urinary alkalinizing agents can increase blood levels and potentiate the action of amphetamine.
Intervention	Co-administration of LISDEXA S.K. 10 MG/ML ORAL SOLUTION and urinary alkalinizing agents should be avoided.
Acidifying Agents	
Clinical Impact	Urinary acidifying agents can lower blood levels and efficacy of amphetamines.
Intervention	Increase dose based on clinical response.
Tricyclic Antidepressants	
Clinical Impact	May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.
Intervention	Monitor frequently and adjust or use alternative therapy based on clinical response.

7.2 Drugs Having No Clinically Important Interactions with LISDEXA S.K. 10 MG/ML ORAL SOLUTION

From a pharmacokinetic perspective, no dose adjustment of LISDEXA S.K. 10 MG/ML ORAL SOLUTION.is necessary when LISDEXA S.K. 10 MG/ML ORAL SOLUTION is co-administered with guanfacine, venlafaxine, or omeprazole. In addition, no dose adjustment of guanfacine or venlafaxine is needed when LISDEXA S.K. 10 MG/ML ORAL SOLUTION is co-administered *[see Clinical Pharmacology (12.3)]*.

From a pharmacokinetic perspective, no dose adjustment for drugs that are substrates of CYP1A2 (e.g. theophylline, duloxetine, melatonin), CYP2D6 (e.g. atomoxetine, desipramine, venlafaxine), CYP2C19 (e.g. omeprazole, lansoprazole, clobazam), and CYP3A4 (e.g. midazolam, pimozide, simvastatin) is necessary when LISDEXA S.K. 10 MG/ML ORAL SOLUTION is co-administered *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data from published literature and postmarketing reports on use of Lisdexamfetamine Dimesylate 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 embryo-fetal 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.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Amphetamines, such as Lisdexamfetamine Dimesylate , 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

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/m2 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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION.

8.4 Pediatric Use

ADHD

Safety and effectiveness of Lisdexamfetamine Dimesylate 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)]*.

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

BED

Safety and effectiveness of Lisdexamfetamine Dimesylate 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 LISDEXA S.K. 10 MG/ML ORAL SOLUTION , 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), 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/m2 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/m2 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 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 m2), the maximum dose should not exceed 50 mg/day. The maximum recommended dose in ESRD (GFR < 15 mL/min/1.73 m2) patients is 30 mg/day *[see Clinical Pharmacology (12.3)]*.

Lisdexamfetamine and d-amphetamine are not dialyzable.

9 DRUG ABUSE AND DEPENDENCE

9.1 LISDEXA S.K. 10 MG/ML ORAL SOLUTION contains lisdexamfetamine

Lisdexamfetamine is a prodrug of amphetamine.

9.2 Abuse

LISDEXA S.K. 10 MG/ML ORAL SOLUTION 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)]*. LISDEXA S.K. 10 MG/ML ORAL SOLUTION 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 drug 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 Lisdexamfetamine Dimesylate , 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 Lisdexamfetamine Dimesylate 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 and 200 mg of diethylpropion hydrochloride). 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

LISDEXA S.K. 10 MG/ML ORAL SOLUTION 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 of CNS stimulants including LISDEXA S.K. 10 MG/ML ORAL SOLUTION dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

Tolerance

LISDEXA S.K. 10 MG/ML ORAL SOLUTION 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:

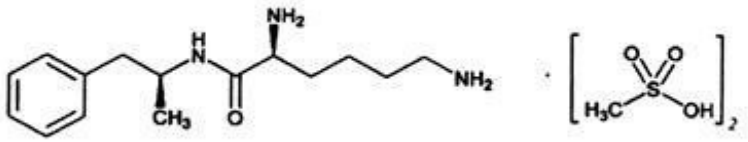
- Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden cardiac death. Takotsubo cardiomyopathy may develop.
- CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin syndrome, seizures, cerebral vascular accidents, and coma may occur.
- Life-threatening hyperthermia (temperatures greater than 40ºC) and rhabdomyolysis may develop.

Overdose Management

Consider the possibility of multiple drug ingestion. The pharmacokinetic profile of LISDEXA S.K. 10 MG/ML ORAL SOLUTION should be considered when treating patients with overdose.Lisdexamfetamine and d-amphetamine are not dialyzable. Consider contacting a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

LISDEXA S.K. 10 MG/ML ORAL SOLUTION (lisdexamfetamine dimesylate), a CNS stimulantis a once-a-day oral administration. The chemical designation for lisdexamfetamine dimesylate is (2S)-2,6-diamino-N-[(1S)- 1-methyl-2- phenylethyl] hexanamide dimethanesulfonate. The molecular formula is C15H25N3O·(CH4O3S)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).

LISDEXA S.K. 10 MG/ML ORAL SOLUTION contain 10 mg of lisdexamfetamine dimesylate in each ml.

Pharmacotherapeutic group: Psychoanaleptics, Centrally Acting Sympathomimetics, ATC code: N06BA12.

Inactive ingredients:
Propylene glycol
Sodium dihydrogen phosphate dihydrate
Disodium phosphate dihydrate
Sodium methyl parahydroxybenzoate
Saccharin sodium
Sodium propyl parahydroxybenzoate
Hydrochloric acid, cone.
Sodium hydroxide
Purified water

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lisdexamfetamine is a prodrug of dextroamphetamine. Amphetamines are non-

catecholamine 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

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 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

After oral administration, lisdexamfetamine dimesylate is rapidly absorbed from the gastrointestinal tract of healthy adults and children (6 to 12 years) with ADHD, thought to be mediated by the high capacity PEPT1 transporter.

Effect of food on formulation

Food does not affect the observed AUC and Cmax of dexamfetamine in healthy adults after single-dose oral administration of 70 mg lisdexamfetamine dimesylate but prolongs Tmax by approximately 1 hour (from 3.8 hours at fasted state to 4.7 hours after a high fat meal). After an 8-hour fast, the AUCs for dexamfetamine following oral administration of lisdexamfetamine dimesylate in solution and as intact capsules were equivalent

Elimination

Following the oral administration of a 70 mg capsule dose of radiolabelled 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 faeces over a period of 120 hours. Of the radioactivity recovered in the urine 42% of the dose was related to amfetamine, 25% to hippuric acid, and 2% intact lisdexamfetamine. 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 studies of lisdexamfetamine dimesylate in volunteers. The half-life of dexamfetamine is 11 hours.

Metabolism
Lisdexamfetamine is converted to dextroamphetamine and l-lysine primarily in blood due to the hydrolytic activity of red blood cells after oral administration, lisdexamfetamine.
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*:

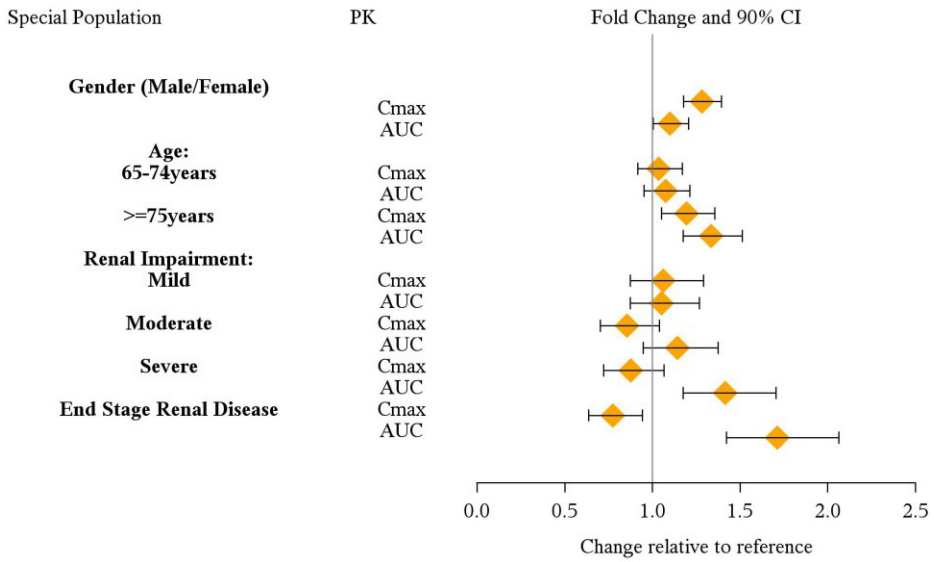
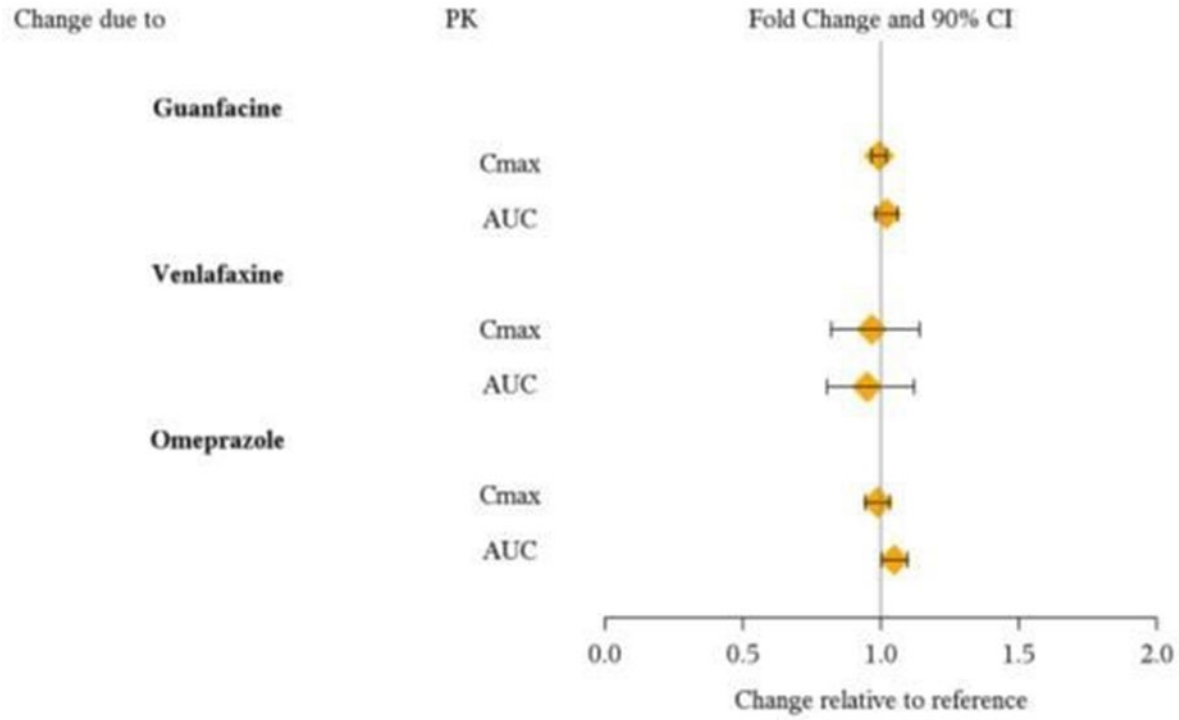


*Figure 1 shows the geometric mean ratios and the 90% confidence limits for C_{max} and AUC of d-amphetamine. Comparison for gender uses males as the reference. Comparison for age uses 55-64 years as the reference.

Drug Interaction Studies

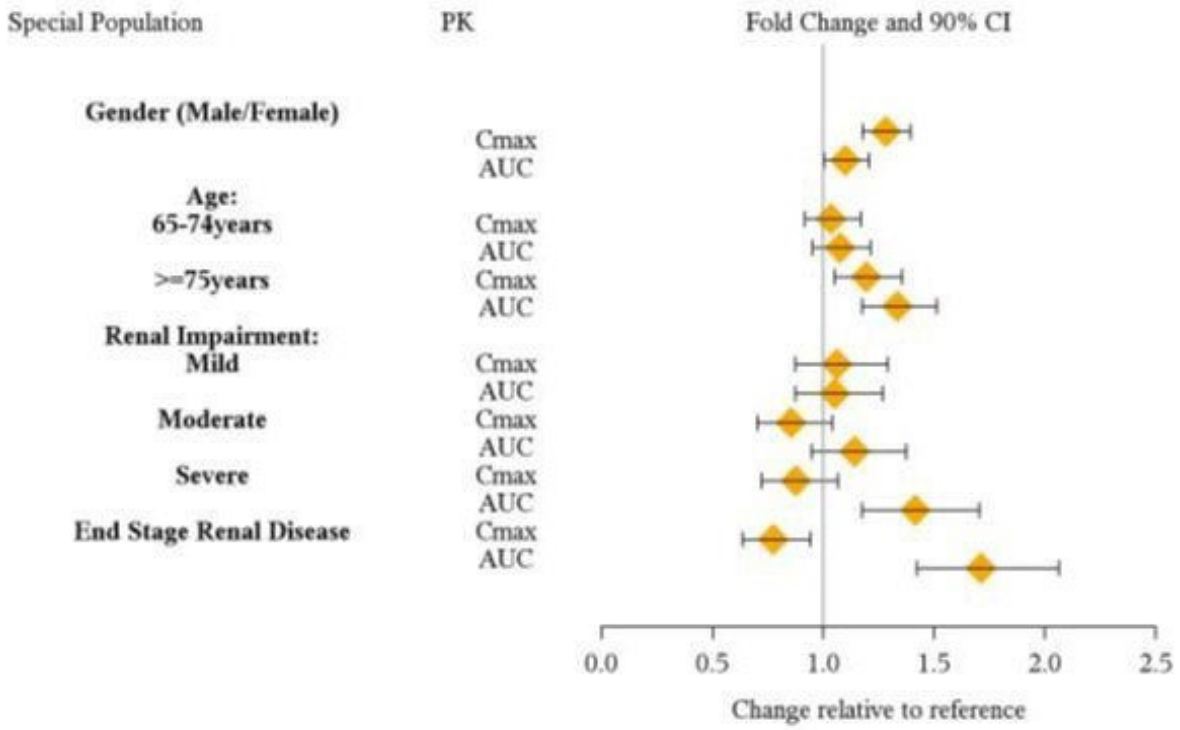
Effects of other drugs on the exposures of dextroamphetamine are summarized in Figure 2.

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.

Figure 3 Effect of Lisdexamfetamine Dimesylate on Other Drugs:



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

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 capsules 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 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 7). 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 capsules (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 capsules 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 capsules(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 capsules (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 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).

Patients Ages 6 to 17 Years Old: 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 and adolescents 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 capsules(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 capsulesfor 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 ADHD-RS ≤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 ADHD- RS 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 capsulesor 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 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 capsules 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 7, 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 capsules 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).

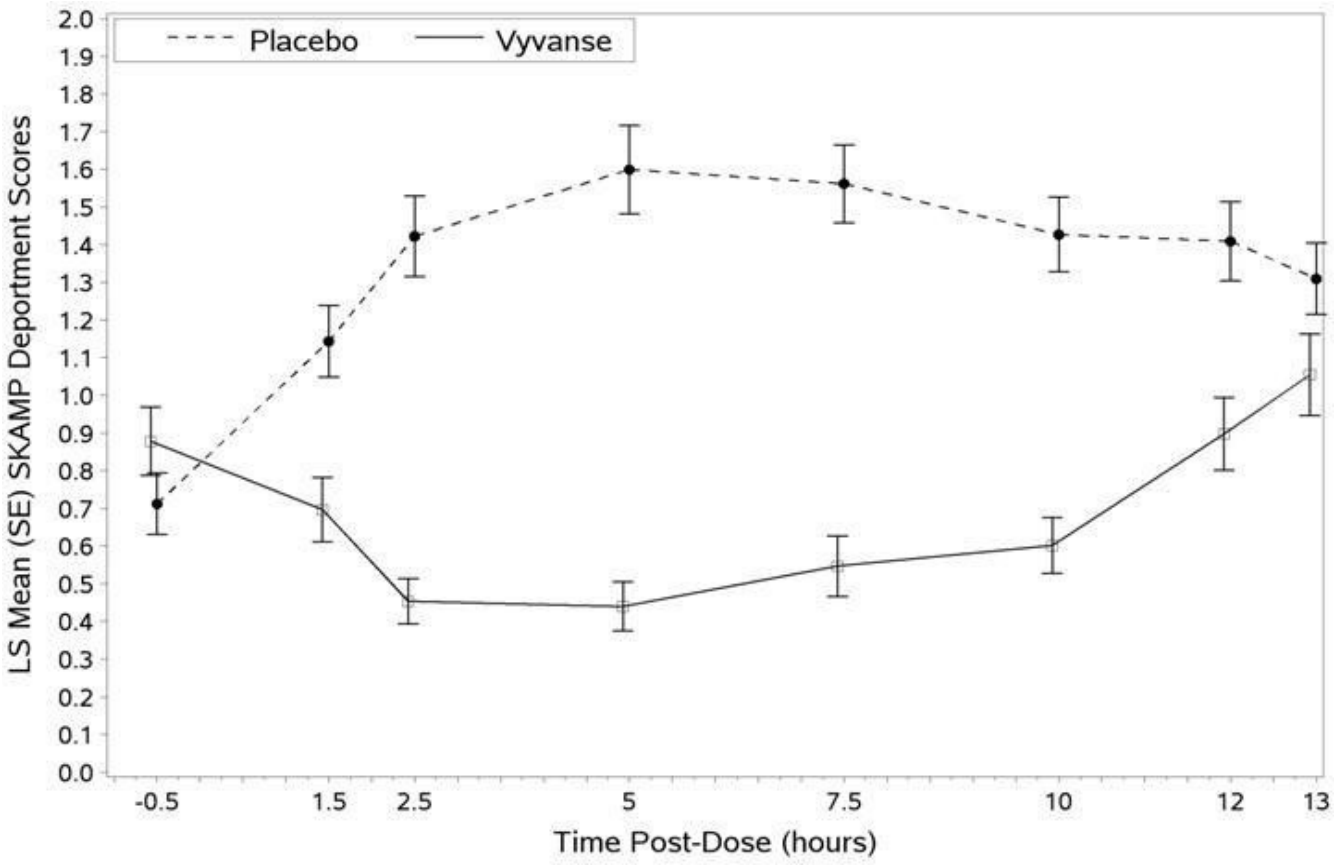
Table 6: Summary of Primary Efficacy Results from Short-term Studies of Lisdexamfetamine Dimesylate in Pediatric Patients (Ages 6 to 17) and Adults with ADHD

Study Number (Age range)	Primary Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo- subtracted Differencea (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)*	-- [b]	0.8 (0.1) [d]	-0.9 (-1.1, -0.7)
		Placebo	-- [b]	1.7 (0.1) [d]	--
Study 3 (6 – 12 years)	Average SKAMP-DS	Lisdexamfetamine Dimesylate (30, 50 or 70 mg/day)*	0.9 (1.0)[c]	0.7 (0.1)[d]	-0.7 (-0.9, -0.6)
		Placebo	0.7 (0.9)[c]	1.4 (0.1)[d]	--
Study 4 (13 – 17 years)	ADHD-RS-IV	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	ADHD-RS-IV	Lisdexamfetamine Dimesylate (30	40.5 (6.2)	-16.2 (1.1)	-8.0 (-11.5, -4.6)

years)		mg/day)*			
		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)	--
Study 8 (18 – 55 years)	Average PERMP	Lisdexamfetamine Dimesylate (30, 50 or 70 mg/day)*	260.1 (86.2)[c]	312.9 (8.6)[d]	23.4 (15.6, 31.2)
		Placebo	261.4 (75.0)[c]	289.5 (8.6)[d]	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
[b] Pre-dose SKAMP-DS was not collected.
[c] Pre-dose SKAMP-DS (Study 3) or PERMP (Study 8) total score, averaged over both periods.
[d] 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.
* Doses statistically significantly superior to placebo.

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

Figure 5 Kaplan-Meier Estimated Proportion of Patients with Treatment Failure for Pediatric Patients Ages 6 to17 (Study 6)

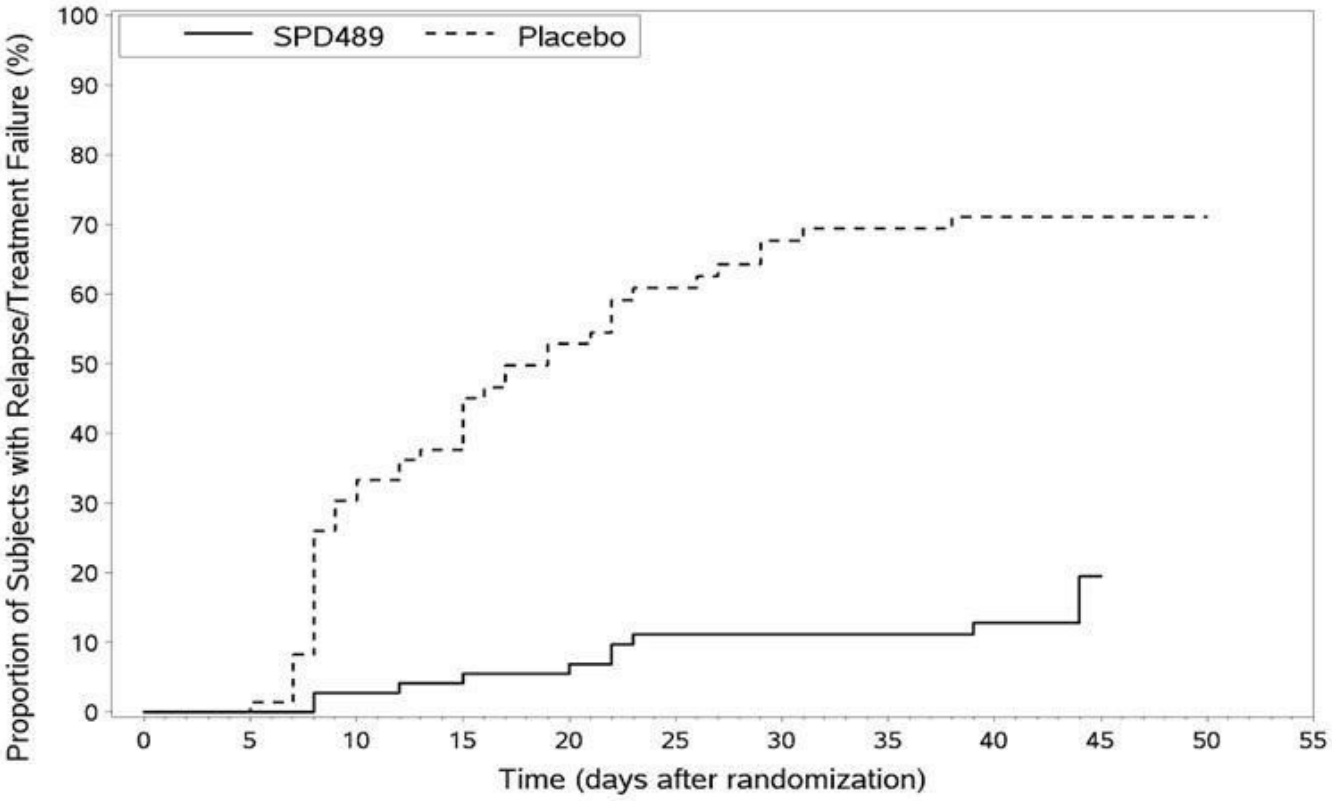
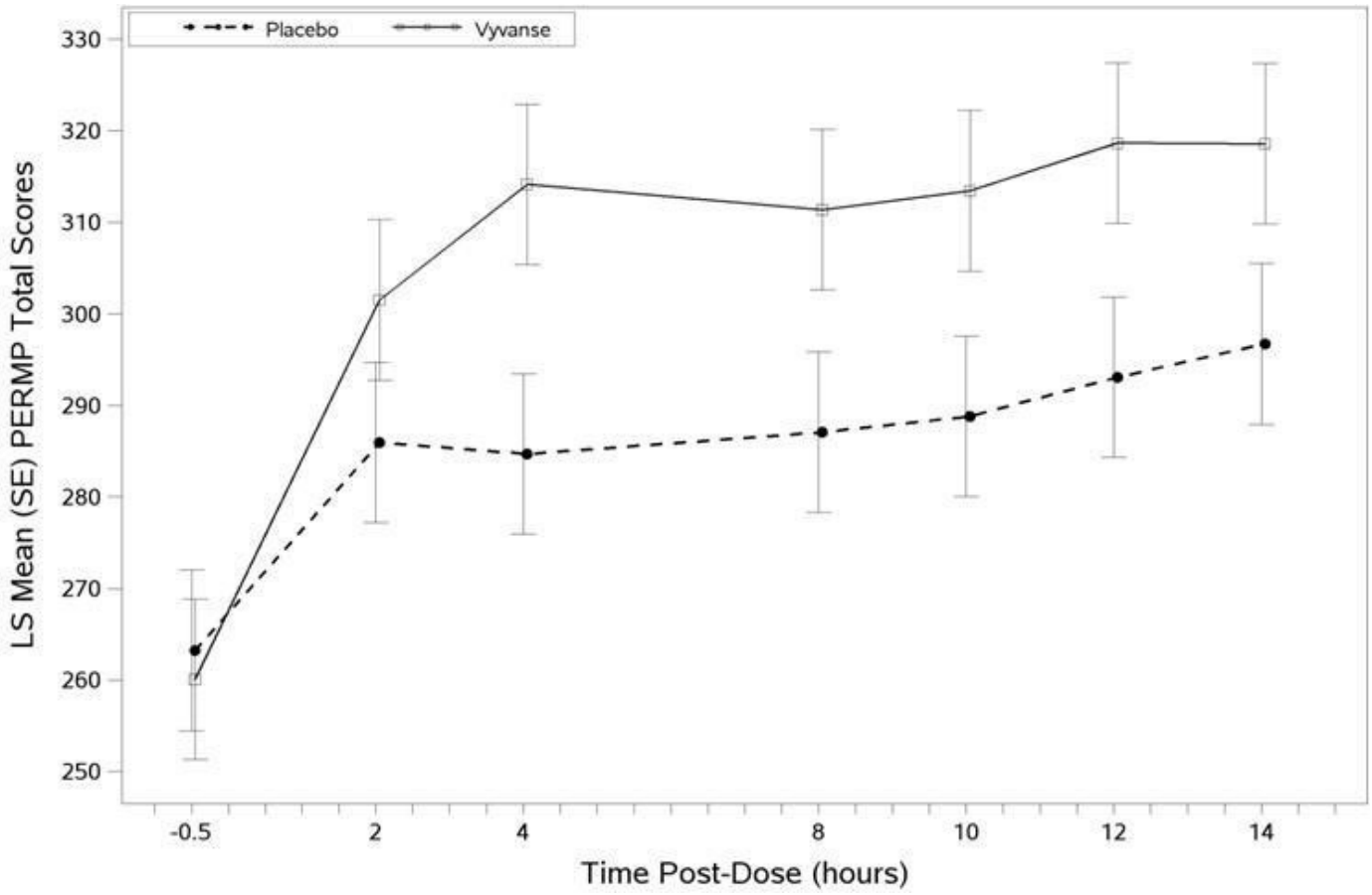
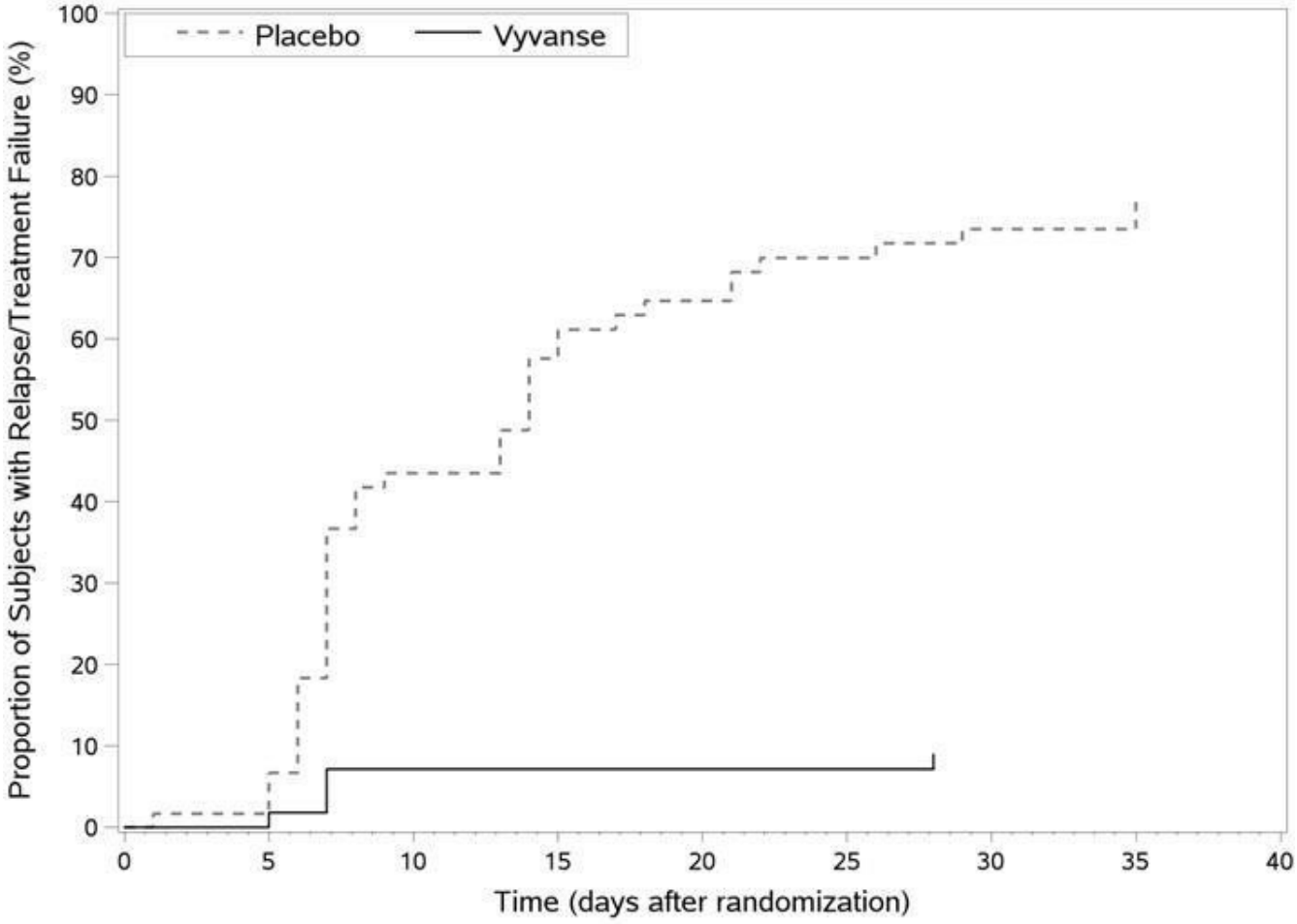


Figure 6 LS Mean (SE) PERMP Total Score by Treatment and Time-point for Adults Ages 18 to 55 with ADHD after 1 Week of Double Blind Treatment (Study 8)



Higher score on the PERMP scale indicates less severe symptoms.

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 capsules 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.

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 capsules 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 capsules 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

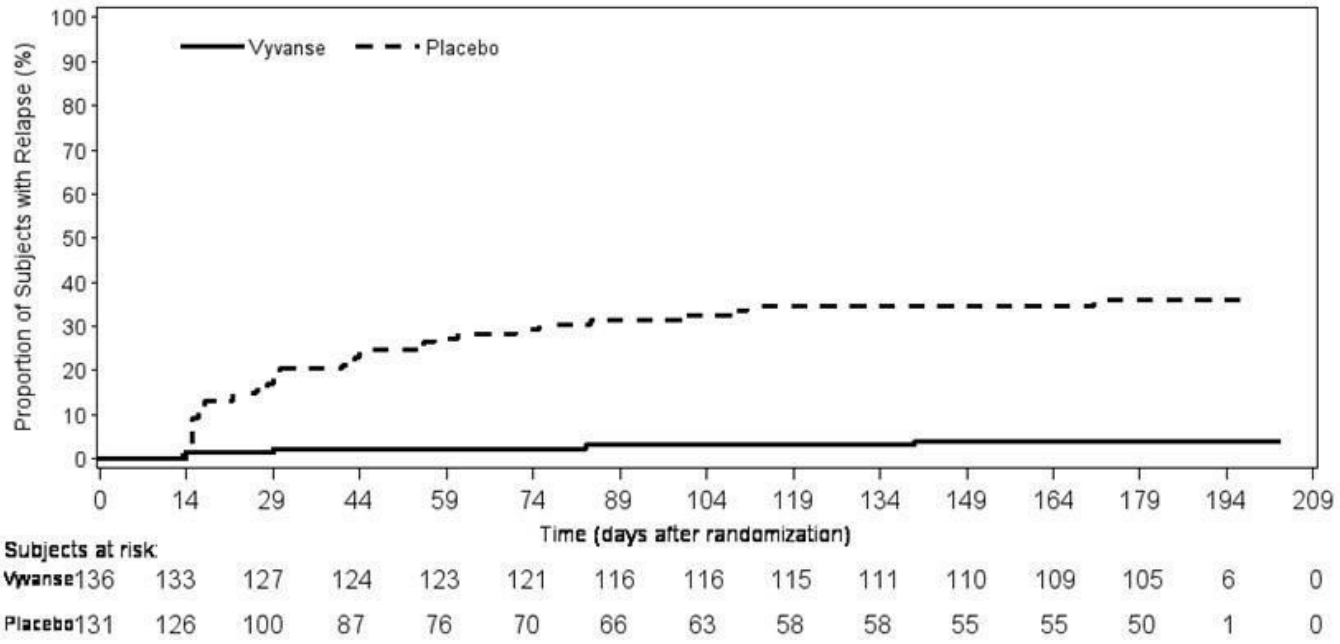
Study Number	**Treatment Group**	**Primary Efficacy Measure: Binge Days per Week at Week 12**		
		Mean Baseline Score (SD)	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference[a] (95% CI)**
Study 11	Lisdexamfetamine Dimesylate (50 or 70 mg/day)*	4.79 (1.27)	-3.87 (0.12)	-1.35 (-1.70, -1.01)
	Placebo	4.60 (1.21)	-2.51 (0.13)	--
Study 12	Lisdexamfetamine Dimesylate (50 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.
[a] 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 capsules 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 capsules 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 patients who had an initial response during the open-label period and then continued on Lisdexamfetamine Dimesylate capsules 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 Proportion 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.

15 HOW SUPPLIED/STORAGE AND HANDLING

15.1 How Supplied

LISDEXA S.K. 10 MG/ML ORAL SOLUTION
The solution is clear, colourless.
Amber glass bottle sealed with a child-proof and tamper evident plastic cap, containing

100 mL oral solution.
A dosing syringe and a plastic plug that is able to fit on the bottle as well as to adopt applicator are also provided. The dosing syringe has 8 mL and the graduation is in steps of 0.1 mL.

<u>To open the bottle and use the syringe</u>

- The bottle comes with a child-proof, tamper evident cap, and should be opened as follows:
  - Push the plastic screw cap down while turning it counter clockwise.
  - Remove the unscrewed cap.
- Open the bottle and, at first use, insert the Press-In Bottle Adapter (PIBA) firmly into the bottle neck (Fig. 1)
- The plunger of the syringe should be at the bottommost position to remove excess air.
- Insert the syringe firmly into the PIBA.
- The bottle should be turned upside down in order to fill the syringe. While holding the syringe in place, the plunger should be pulled down gently and the medicine should be drawn to the correct mark on the syringe (Fig. 2)
- The bottle should be turned upright again, and the filled syringe must be removed from the adaptor by gentle twisting (Fig. 3)
- Remove the filled syringe from the bottle in upright position.
- Empty the syringe into a glass of tap water, cola drink or fruit juice or directly into the patient's mouth by sliding the upper ring down and drink it immediately; tea should not be used to dilute the lisdexamfetamine solution due to incompatibility observed after dilution of this medicinal product with tea. Any mixing outside the recommendations is the responsibility of the health care professional or the user.
- After use, the bottle cap must be replaced leaving the adaptor in place.
- The syringe should be rinsed and washed with cold or warm water after each use and dried completely before the next use.

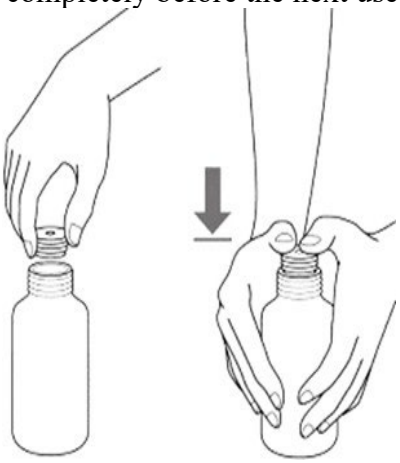


Fig. 1

Fig. 2

Fig. 3

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

15.2 Storage and Handling:

Do not store above 30°C

After first opening of the bottle

Do not use more than 30 days.
Do not store above 25°C.

16 MANUFACTURER

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Malta Life Sciences Park, Building 1, Level 4 ,Sir Temi Zammit Buildings San Gwann, SGN 3000, Malta.

17 License Holder

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94 Igal Alon St., Tel-Aviv 6789139, Israel.

18 Registration number

LISDEXA S.K. 10 MG/ML ORAL SOLUTION :177-13-37921

Approved on April 2025.

SK_LISD_OS_SPC_04_24_V1