SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Attent XR 5 mg
Attent XR 10 mg
Attent XR 15 mg
Attent XR 20 mg
Attent XR 25 mg
Attent XR 30 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Attent XR contains mixed salts of a single-entity amphetamine, a CNS stimulant.
Attent XR contains equal amounts (by weight) of four salts: dextroamphetamine sulfate, amphetamine sulfate, dextroamphetamine saccharate and amphetamine (D,L)-aspartate monohydrate. This results in a 3.1:1 mixture of dextro- to levo- amphetamine base equivalent.

Each capsule contains:

Capsule Strength	**5 mg**	**10 mg**	**15 mg**	**20 mg**	**25 mg**	**30 mg**
Dextroamphetamine Saccharate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine (D,L)-Aspartate Monohydrate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Dextroamphetamine Sulfate, USP	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine Sulfate, USP	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Total amphetamine base equivalence	3.1 mg	6.3 mg	9.4 mg	12.5 mg	15.6 mg	18.8 mg
d-amphetamine base equivalence	2.4 mg	4.7 mg	7.1 mg	9.5 mg	11.9 mg	14.2 mg
l-amphetamine base equivalence	0.75 mg	1.5 mg	2.3 mg	3.0 mg	3.8 mg	4.5 mg

For special warnings and precautions relating to the composition see section 7.11 under "excipients with known effect". For the list of excipients, see section 16.

3. PHARMACEUTICAL FORM

Extended-release capsules for oral administration.

Attent XR (dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, amphetamine sulfate extended-release capsules = MAS ER capsules) contains two types of beads (immediate-release and delayed release) which prolong the release of amphetamine compared to Attent (dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, amphetamine sulfate immediate-release tablet formulation= MAS IR).

WARNING: ABUSE, MISUSE AND DEPENDENCE

Attent XR capsules have 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 Attent XR capsules, can result in overdose and death *[see Overdosage]* and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.
Before prescribing Attent XR capsules, assess each patient's risk of abuse, misuse and addiction.
Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused Throughout Attent XR capsules 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 (7) and Drug Abuse and Dependence (11)]*.

4 THERAPEUTIC INDICATIONS

Attent XR Capsules are indicated for the treatment of attention deficit hyperactivity disorder (ADHD).

Attention Deficit Hyperactivity Disorder

The efficacy of MAS ER in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12, one controlled trial in adolescents aged 13 to 17, and one controlled trial in adults who met DSM-IV® criteria for ADHD *[see Clinical Studies (15)]*.

A diagnosis of ADHD (DSM-IV®) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations
Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV® characteristics.

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

Long-Term Use
The effectiveness of MAS ER capsules for long-term use, i.e., for more than 3 weeks in children and 4 weeks in adolescents and adults, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Attent XR capsules for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

5 DOSAGE AND ADMINISTRATION

5.1 Important Information Prior to Initiating Treatment
Prior to initiating treatment with Attent XR capsules, assess for the presence of cardiac disease (e.g., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) *[see Warnings and*

Precautions (7)].

Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs for abuse and overdose, and periodically re-evaluate the need for Attent XR use *[see Warnings and Precautions (7), Drug Abuse and Dependence (11)]*.

5.2 Dosing Considerations for All Patients
Individualize the dosage according to the therapeutic needs and response of the patient. Administer Attent XR capsules at the lowest effective dosage.

Based on bioequivalence data, patients taking divided doses of MAS IR, (for example, twice daily), may be switched to MAS ER capsules at the same total daily dose taken once daily. Titrate at weekly intervals to appropriate efficacy and tolerability as indicated.

Attent XR may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce. If the patient is using the sprinkle administration method, the sprinkled applesauce should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and patients should not take anything less than one capsule per day.

Attent XR may be taken with or without food.

Attent XR should be given upon awakening. Afternoon doses should be avoided because of the potential for insomnia.

Where possible, Attent XR therapy should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

5.3 Children
In children with ADHD who are 6 to 12 years of age and are either starting treatment for the first time or switching from another medication, start with 10 mg once daily in the morning; daily dosage may be adjusted in increments of 5 mg or 10 mg at weekly intervals. When in the judgment of the clinician a lower initial dose is appropriate, patients may begin treatment with 5 mg once daily in the morning. The maximum recommended dose for children 6 to 12 years of age is 30 mg/day; doses greater than 30 mg/day have not been studied in children. MAS ER capsules have not been studied in children under 6 years of age.

5.4 Adolescents
The recommended starting dose for adolescents with ADHD who are 13 to 17 years of age and are either starting treatment for the first time or switching from another medication is 10 mg/day. The dose may be increased to 20 mg/day after one week if ADHD symptoms are not adequately controlled.

5.5 Adults
In adults with ADHD who are either starting treatment for the first time or switching from another medication, the recommended dose is 20 mg/day.

5.6 Dosage in Patients with Renal Impairment
In adult patients with severe renal impairment (GFR 15 to < 30 mL/min/1.73m^2), the recommended dose is 15 mg once daily in the morning. In pediatric patients (6 to 17 years of age) with severe renal impairment, the recommended dose is 5 mg once daily. The maximum dose for children 6 to 12 years of age with severe renal

impairment is 20 mg once daily. Attent XR capsules are not recommended in patients with end stage renal disease (ESRD) (GFR < 15 mL/min/1.73m^2) *[see Use in Specific Populations (10), Clinical Pharmacology (13)]*.

6 CONTRAINDICATIONS

Attent XR administration is contraindicated in patients:

- known to be hypersensitive to amphetamine, or other components of Attent XR capsules. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other amphetamine products *[see Adverse Reactions (8)]*
- 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 (7) and Drug Interactions (9)]*
- Hypersensitivity to the active substance or to any of the excipients listed in section 16.

7 WARNINGS AND PRECAUTIONS

7.1 Abuse Misuse and Addiction

Attent XR capsules have a high potential for abuse and misuse. The use of Attent XR capsules expose individuals to the risks of abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Attent XR capsules can be diverted for non-medical use into illicit channels or distribution *[see Drug Abuse and Dependence (11)]*. Misuse and abuse of CNS stimulants, including Attent XR capsules, can result in overdose and death *[see Overdosage (12)]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.
Before prescribing Attent XR capsules, 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 Attent XR in a safe place, preferably locked, and instruct patients to not give Attent XR to anyone else. .
Throughout Attent XR treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

7.2 Risks to Patients with Serious Cardiac Disease Cardiovascular Reactions

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 Attent XR capsules use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease , or other serious cardiac disease.

7.3 Increased Blood Pressure and Heart Rate

CNS Stimulants may cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately3 to 6 bpm). Monitor all Attent XR patients for hypertension and tachycardia .

7.4 Psychiatric Adverse Events

Exacerbation of Pre-Existing Psychosis
Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with pre-existing psychotic disorder.

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

New Psychotic or Manic Symptoms
CNS stimulants, at 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 approximately0.1% of CNS stimulant-treated patients compared to 0% of placebo-treated patients. If such symptoms occur, consider discontinuing Attent XR capsules.

7.5 Long-Term Suppression of Growth in Pediatric Patients

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in Attent XR treated pediatric patients treated with CNS stimulants. .
In a controlled trial of MAS ER in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was –1.1 lbs. and –2.8 lbs., respectively, for patients receiving 10 mg and 20 mg MAS ER. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment. Chronic use of amphetamines can be expected to cause a similar suppression of growth.

Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

7.6 Seizures

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

7.7 Peripheral Vasculopathy, Including Raynaud's Phenomenon

CNS stimulants, including MAS ER, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very 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 dosage of CNS stimulants in all age groups throughout the course of treatment. Signs and symptoms generally improve after dosage reduction or discontinuation of the CNS stimulant.
Careful observation for digital changes is necessary during MAS ER treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for MAS ER treated patients who develop signs or symptoms of peripheral vasculopathy.

7.8 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 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*

(9)]. Amphetamines and amphetamine derivatives are known to be metabolized, to some degree, by cytochrome P450 2D6 (CYP2D6) and display minor inhibition of CYP2D6 metabolism *[see Clinical Pharmacology (13)]*. The potential for a pharmacokinetic interaction exists with the co-administration of CYP2D6 inhibitors which may increase the risk with increased exposure to MAS ER. In these situations, consider an alternative non-serotonergic drug or an alternative drug that does not inhibit CYP2D6 *[see Drug Interactions (9)]*. 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 Attent XR with MAOI drugs is contraindicated *[see Contraindications (6)]*.

Discontinue treatment with Attent XR and any concomitant serotonergic agents immediately if symptoms of serotonin syndrome occur and initiate supportive symptomatic treatment. Concomitant use of Attent XR with other serotonergic drugs or CYP2D6 inhibitors should be used only if the potential benefit justifies the potential risk. If clinically warranted, consider initiating Attent XR with lower doses, monitoring patients for the emergence of serotonin syndrome during drug initiation or titration, and informing patients of the increased risk for serotonin syndrome.

7.9 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 also been
reported. Before initiating MAS ER assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor MAS ER treated patients for the emergence or worsening of tics or Tourette's syndrome and discontinue treatment if clinically appropriate.

7.10 Prescribing and Dispensing

The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Attent XR should be used with caution in patients who use other sympathomimetic drugs.

7.11 Excipients with Known Effect

This medicine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

7.12 Effect on ability to drive and use machines

This medicine may impair the ability of the patient to drive or to engage in potentially hazardous activities such as operating machinery. The patient should therefore be cautioned accordingly

8 ADVERSE REACTIONS

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

- Abuse, Misuse, and Addiction *[see Boxed Warning, Warnings and Precautions (7.1), Drug Abuse and Dependence (11)]*
- Risks to Patients with Serious Cardiac Disease *[see Warnings and Precautions (7.2)]*

- Increased Blood Pressure and Heart Rate *[see Warnings and Precautions (7.3)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (7.4)]*
- Long-Term Suppression of Growth in Pediatric Patients *[see Warnings and Precautions (7.5)]*
- Seizures *[see Warnings and Precautions (7.6)]*
- Peripheral Vasculopathy, including Raynaud's Phenomenon *[see Warnings and Precautions (7.7)]*
- Serotonin Syndrome *[see Warnings and Precautions (7.8)]*
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome *[see Warnings and Precautions (7.9)]*

8.1 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.

The premarketing development program for MAS ER included exposures in a total of 1315 participants in clinical trials (635 pediatric patients, 350 adolescent patients, 248 adult patients, and 82 healthy adult subjects). Of these, 635 patients (ages 6 to 12) were evaluated in two controlled clinical studies, one open-label clinical study, and two single-dose clinical pharmacology studies (N= 40). Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse reactions during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse reactions.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed.

<u>Adverse Reactions Leading to Discontinuation of Treatment</u>
In two placebo-controlled studies of up to 5 weeks duration among children with ADHD, 2.4% (10/425) of MAS ER-treated patients discontinued due to adverse reactions (including 3 patients with loss of appetite, one of whom also reported insomnia) compared to 2.7% (7/259) receiving placebo.

The most frequent adverse reactions leading to discontinuation of MAS ER in controlled and uncontrolled, multiple-dose clinical trials of children (N=595) were anorexia (loss of appetite) (2.9%), insomnia (1.5%), weight loss (1.2%), emotional lability (1%), and depression (0.7%). Over half of these patients were exposed to MAS ER for 12 months or more.

In a separate placebo-controlled 4-week study in adolescents with ADHD, five patients (2.1%) discontinued treatment due to adverse events among MAS ER-treated patients (N=233) compared to none who received placebo (N=54). The most frequent adverse event leading to discontinuation and considered to be drug-related (i.e. leading to discontinuation in at least 1% of MAS ER-treated patients and at a rate at least twice that of placebo) was insomnia (1.3%, n=3).

In one placebo-controlled 4-week study among adults with ADHD with doses 20 mg to 60 mg, 23 patients (12.0%) discontinued treatment due to adverse events among MAS ER-treated patients (N=191) compared to one patient (1.6%) who received placebo (N=64). The most frequent adverse events leading to discontinuation and considered to be drug-related (i.e. leading to discontinuation in at least 1% of MAS ER-treated patients and at a rate at least twice that of placebo) were insomnia (5.2%, n=10), anxiety (2.1%, n=4), nervousness (1.6%, n=3), dry mouth (1.6%, n=3), anorexia (1.6%, n=3), tachycardia (1.6%, n=3), headache (1.6%, n=3), and asthenia (1.0%, n=2).

Adverse Reactions Occurring in Controlled Trials

Adverse reactions reported in a 3-week clinical trial of children and a 4-week clinical trial in adolescents and adults, respectively, treated with MAS ER or placebo are presented in the tables below.

Table 1 Adverse Reactions Reported by 2% or More of Children (6 to 12 Years Old) Receiving MAS ER with Higher Incidence Than on Placebo in a 584-Patient Clinical Study

Body System	Preferred Term	MAS ER (n=374)	Placebo (n=210)
General	Abdominal Pain (stomachache)	14%	10%
	Fever	5%	2%
	Infection	4%	2%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Vomiting	7%	4%
	Nausea	5%	3%
	Dyspepsia	2%	1%
Nervous System	Insomnia	17%	2%
	Emotional Lability	9%	2%
	Nervousness	6%	2%
	Dizziness	2%	0%
Metabolic/Nutritional	Weight Loss	4%	0%

Table 2 Adverse Reactions Reported by 5% or More of Adolescents (13 to 17 Years Old) Weighing ≤ 75 kg/165 lbs Receiving MAS ER with Higher Incidence Than Placebo in a 287 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	MAS ER (n=233)	Placebo (n=54)
General	Abdominal Pain (stomachache)	11%	2%
Digestive System	Loss of Appetite [b]	36%	2%
Nervous System	Insomnia [b]	12%	4%
	Nervousness	6%	6%[a]
Metabolic/Nutritional	Weight Loss [b]	9%	0%

*Included doses up to 40 mg

[a] Appears the same due to rounding

[b] Dose-related adverse reactions

Note: The following reactions did not meet the criterion for inclusion in Table 2 but were reported by 2% to 4% of adolescent patients receiving MAS ER with a higher incidence than patients receiving placebo in this study: accidental injury, asthenia (fatigue), dry mouth, dyspepsia, emotional lability, nausea, somnolence, and vomiting.

Table 3 Adverse Reactions Reported by 5% or More of Adults Receiving MAS ER with Higher Incidence Than on Placebo in a 255 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	MAS ER (n=191)	Placebo (n=64)
General	Headache	26%	13%
	Asthenia	6%	5%
Digestive System	Dry Mouth	35%	5%
	Loss of Appetite	33%	3%
	Nausea	8%	3%
	Diarrhea	6%	0%
Nervous System	Insomnia	27%	13%
	Agitation	8%	5%
	Anxiety	8%	5%
	Dizziness	7%	0%
	Nervousness	13%	13%[a]
Cardiovascular System	Tachycardia	6%	3%
Metabolic/Nutritional	Weight Loss	10%	0%
Urogenital System	Urinary Tract Infection	5%	0%

*Included doses up to 60 mg.

[a] Appears the same due to rounding

Note: The following reactions did not meet the criterion for inclusion in Table 3 but were reported by 2% to 4% of adult patients receiving MAS ER with a higher incidence than patients receiving placebo in this study: infection, photosensitivity reaction, constipation, tooth disorder (e.g., teeth clenching, tooth infection), emotional lability, libido decreased, somnolence, speech disorder (e.g., stuttering, excessive speech), palpitation, twitching, dyspnea, sweating, dysmenorrhea, and impotence.

Hypertension

In a controlled 4-week outpatient clinical study of adolescents with ADHD, isolated systolic blood pressure elevations ≥15 mmHg were observed in 7/64 (11%) placebo-treated patients and 7/100 (7%) patients receiving MAS ER 10 or 20 mg. Isolated elevations in diastolic blood pressure ≥8 mmHg were observed in 16/64 (25%) placebo-treated patients and 22/100 (22%) MAS ER-treated patients. Similar results were observed at higher doses*[see Warnings and Precautions (7)]*.

In a single-dose pharmacokinetic study in 23 adolescents with ADHD, isolated increases in systolic blood pressure (above the upper 95% CI for age, gender, and stature) were observed in 2/17 (12%) and 8/23 (35%), subjects administered 10 mg and 20 mg MAS ER, respectively. Higher single doses were associated with a greater increase in systolic blood pressure. All increases were transient, appeared maximal at 2 to 4 hours post dose and not associated with symptoms.

8.2 Adverse Reactions Associated with the Use of MAS ER or MAS IR

The following adverse reactions have been identified during post-approval use of MAS ER, or MAS IR. 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.

Cardiovascular

Palpitations. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System

Psychotic episodes at recommended doses, overstimulation, restlessness, irritability, euphoria, dyskinesia, dysphoria, depression, tremor, motor and verbal tics, aggression, anger, logorrhea, dermatillomania, paresthesia (including formication), and bruxism.

Eye Disorders
Vision blurred, mydriasis.

Gastrointestinal
Unpleasant taste, constipation, intestinal ischemia, and other gastrointestinal disturbances.

Allergic
Urticaria, rash, hypersensitivity reactions including angioedema and anaphylaxis. Serious skin rashes, including Stevens-Johnson Syndrome and toxic epidermal necrolysis have been reported.

Endocrine
Impotence, changes in libido, frequent or prolonged erections.

Skin
Alopecia.

Vascular Disorders
Raynaud's phenomenon.

Musculoskeletal and Connective Tissue Disorders
Rhabdomyolysis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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

9 DRUG INTERACTIONS

9.1 Clinically Important Interactions with Amphetamines

Table 4: Drugs Having Clinically Important Interactions with Amphetamines

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.
Intervention	Do not administer MAS ER concomitantly or within 14 days after discontinuing MAOI *[see Contraindications (6)]*.
Serotonergic Drugs	
Clinical Impact	The concomitant use of MAS ER 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 MAS ER initiation or dosage increase. If serotonin syndrome occurs, discontinue MAS ER and the concomitant serotonergic drug(s) *[see Warnings and Precautions (7)]*.
CYP2D6 Inhibitors	
Clinical Impact	The concomitant use of MAS ER and CYP2D6 inhibitors may increase the exposure of MAS ER 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 MAS ER initiation and after a dosage increase. If serotonin syndrome occurs, discontinue MAS ER and the CYP2D6 inhibitor *[see Warnings and Precautions (7) and Overdosage (12)]*.
Alkalinizing Agents	
Clinical Impact	Increase blood levels and potentiate the action of amphetamine.
Intervention	Co-administration of MAS ER and gastrointestinal or urinary alkalinizing agents should be avoided.
Acidifying Agents	
Clinical Impact	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.
Proton Pump Inhibitors	
Clinical Impact	Time to maximum concentration (T_{max}) of amphetamine is decreased compared to when administered alone.
Intervention	Monitor patients for changes in clinical effect and adjust therapy based on clinical response.

9.2 Drug-Laboratory Test Interactions
Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations**.**

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary
Available data from published epidemiologic studies and post marketing reports on use of prescription amphetamine in pregnant women have not identified a drug-associated risk of major birth defects and miscarriage *(see Data)*. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers taking amphetamines during pregnancy *(see Clinical Considerations)*.

No apparent effects on morphological development were observed in embryo-fetal development studies, with oral administration of amphetamine to rats and rabbits during organogenesis at doses 2 and 12 times, respectively, the maximum recommended human dose (MRHD) of 20 mg/day given to adolescents, on a mg/m^2 basis. However, in a pre- and post-natal development study, amphetamine (*d*- to *l*- ratio of 3:1) administered orally 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% to 4% and 15% to 20%, respectively.

Clinical Considerations
Fetal/Neonatal Adverse Reactions

Amphetamines, such as MAS ER, cause vasoconstriction and thereby may decrease placental perfusion. In addition, amphetamines can stimulate uterine contractions, increasing the risk of premature delivery. Infants born to mothers taking amphetamines during pregnancy 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

Amphetamine (*d*- to *l*- enantiomer ratio of 3:1) had no apparent effects on embryofetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 2 and 12 times, respectively, the maximum recommended human dose (MRHD) of 20 mg/day given to adolescents, on a mg/m^2 basis. Fetal malformations and death have been reported in mice following parenteral administration of *d*-amphetamine doses of 50 mg/kg/day (approximately 10 times the MRHD given to adolescents on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A study was conducted in which pregnant rats received daily oral doses of amphetamine (*d*- to *l*- enantiomer ratio of 3:1) of 2, 6, and 10 mg/kg from gestation day 6 to lactation day 20. These doses are approximately 0.8, 2, and 4 times the MRHD of 20 mg/day given to adolescents, on a mg/m^2 basis. 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.

10**.2 Lactation**

Risk Summary

Based on limited case reports in published literature, amphetamine (*d*- or *d*, *l*-) is present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. It is possible that large dosages of amphetamine 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, advise patients that breastfeeding is not recommended during treatment with MAS ER.

10.3 Pediatric Use

MAS ER is indicated for use in children 6 years of age and older.
The safety and efficacy of MAS ER in pediatric patients less than6 years of age have not been established.
Long-term effects of amphetamines in pediatric patients has not been well established.

Long-Term Growth Suppression
Growth should be monitored during treatment with stimulants, including MAS ER, and pediatric patients aged 6 to 17 years who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (7)]*.

Juvenile Animal Toxicity Data
Juvenile rats treated with mixed amphetamine salts early in the postnatal period through sexual maturation demonstrated transient changes in motor activity. Learning and memory was impaired at approximately 6 times the maximum recommended human dose (MRHD) given to children on a mg/m^2 basis. No recovery was seen following a drug free period. A delay in sexual maturation was observed at a dose approximately 6 times the MRHD given to children on a mg/m^2 basis, although there was no effect on fertility.

In a juvenile developmental study, rats received daily oral doses of amphetamine (*d* to *l* enantiomer ratio of 3:1) of 2, 6, or 20 mg/kg on days 7 to 13 of age; from day 14 to approximately day 60 of age these doses were given b.i.d. for total daily doses of 4, 12, or 40 mg/kg. The latter doses are approximately 0.6, 2, and 6 times the MRHD of 30 mg/day, given to children on a mg/m^2 basis. Post dosing hyperactivity was seen at all doses; motor activity measured prior to the daily dose was decreased during the dosing period but the decreased motor activity was largely absent after an 18 day drug-free recovery period. Performance in the Morris water maze test for learning and memory was impaired at the 40 mg/kg dose, and sporadically at the lower doses, when measured prior to the daily dose during the treatment period; no recovery was seen after a 19 day drug-free period. A delay in the developmental milestones of vaginal opening and preputial separation was seen at 40 mg/kg but there was no effect on fertility.

10.4 Geriatric Use

MAS ER has not been studied in the geriatric population.

10.5 Renal Impairment

Due to reduced clearance of amphetamines in patients with severe renal impairment (GFR 15 to <30 mL/min/1.73m^2), the recommended dose should be reduced. MAS ER is not recommended in patients with ESRD (GFR < 15 ml/min/1.73m^2) *[see Dosage and Administration (5), Clinical Pharmacology (13)]*.

d-Amphetamine is not dialyzable.

11 DRUG ABUSE AND DEPENDENCE

11.1 Abuse

MAS ER 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 (7.1)]*. MAS ER 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 healthcare 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 amphetamine may cause increased heart rate, respiratory rate, 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, suicidal or homicidal ideation have also been observed with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including MAS ER, can result in overdose and death *[see Overdosage (12)])]*, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

11.2 Dependence

Physical Dependence
MAS ER 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 a 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 MAS ER include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

Tolerance
MAS ER 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).

12 OVERDOSAGE

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

- Life-threatening hyperthermia (temperatures greater than 104°F) and rhabdomyolysis may develop.
- 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.

Overdose Management
Consult with a Certified Poison Control Center for up to date guidance and advice.
Consider the possibility of multiple drug ingestion.
The pharmacokinetic profile of MAS XR should be considered when treating patients with overdose.
d-Amphetamine is not dialyzable.
Consider contacting a Certified Poison Control Center or a medical toxicologist for
additional overdose management recommendations.

13 CLINICAL PHARMACOLOGY

13.1 Mechanism of Action
Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in ADHD is not known.

13.2 Pharmacodynamics
Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the

release of these monoamines into the extraneuronal space.

13.3 Pharmacokinetics

Pharmacokinetic studies of MAS ER have been conducted in healthy adult and pediatric (children aged 6 to 12 yrs) subjects, and adolescent (13 to 17 yrs) and children with ADHD. Both MAS (immediate-release/ IR) tablets and MAS ER capsules contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of MAS (immediate-release/ IR), the peak plasma concentrations occurred in about 3 hours for both d-amphetamine and l-amphetamine.

The time to reach maximum plasma concentration (T_{max}) for MAS ER is about 7 hours, which is about 4 hours longer compared to MAS (immediate-release/ IR). This is consistent with the extended-release nature of the product.

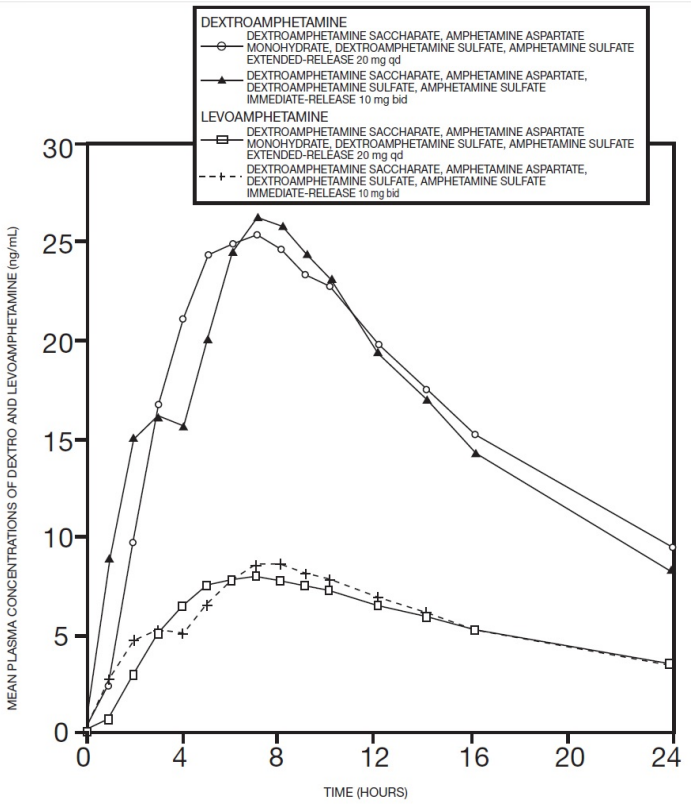

Figure 1 Mean d-amphetamine and l-amphetamine Plasma Concentrations Following Administration of MAS ER 20 mg (8 am) and MAS (immediate-release/ IR) 10 mg Twice Daily (8 am and 12 noon) in the Fed State.

A single dose of MAS ER 20 mg capsules provided comparable plasma concentration profiles of both d-amphetamine and l-amphetamine to MAS (immediate-release/IR) 10 mg twice daily administered 4 hours apart.

The mean elimination half-life for d-amphetamine is 10 hours in adults; 11 hours in adolescents aged 13 to 17 years and weighing less than or equal to 75 kg/165 lbs; and 9 hours in children aged 6 to 12 years. For the l-amphetamine, the mean elimination half-life in adults is 13 hours; 13 to 14 hours in adolescents; and 11 hours in children aged 6 to 12 years. On a mg/kg body weight basis, children have a higher clearance than adolescents or adults (see Special Populations below).

MAS ER demonstrates linear pharmacokinetics over the dose range of 20 to 60 mg in adults and adolescents

weighing greater than 75 kg/165 lbs, over the dose range of 10 to 40 mg in adolescents weighing less than or equal to 75 kg/165 lbs, and 5 to 30 mg in children aged 6 to 12 years. There is no unexpected accumulation at steady state in children.

Food does not affect the extent of absorption of d-amphetamine and l-amphetamine, but prolongs T_{max} by 2.5 hours (from 5.2 hrs at fasted state to 7.7 hrs after a high-fat meal) for d-amphetamine and 2.7 hours (from 5.6 hrs at fasted state to 8.3 hrs after a high fat meal) for l-amphetamine after administration of MAS ER 30 mg. Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted state. Equal doses of MAS ER strengths are bioequivalent.

Metabolism and Excretion

Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4-hydroxyamphetamine, or on the side chain α or β carbons to form alpha-hydroxy-amphetamine or norephedrine, respectively. Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

Amphetamine is known to inhibit monoamine oxidase, whereas the ability of amphetamine and its metabolites to inhibit various P450 isozymes and other enzymes has not been adequately elucidated. *In vitro* experiments with human microsomes indicate minor inhibition of CYP2D6 by amphetamine and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites. However, due to the probability of auto-inhibition and the lack of information on the concentration of these metabolites relative to *in vivo* concentrations, no predications regarding the potential for amphetamine or its metabolites to inhibit the metabolism of other drugs by CYP isozymes *in vivo* can be made.

With normal urine pHs, approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30% to 40% of the dose is recoverable in urine as amphetamine itself. Since amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates. Alkaline urine pHs result in less ionization and reduced renal elimination, and acidic pHs and high flow rates result in increased renal elimination with clearances greater than glomerular filtration rates, indicating the involvement of active secretion. Urinary recovery of amphetamine has been reported to range from 1% to 75%, depending on urinary pH, with the remaining fraction of the dose hepatically metabolized. Consequently, both hepatic and renal dysfunction have the potential to inhibit the elimination of amphetamine and result in prolonged exposures. In addition, drugs that effect urinary pH are known to alter the elimination of amphetamine, and any decrease in amphetamine's metabolism that might occur due to drug interactions or genetic polymorphisms is more likely to be clinically significant when renal elimination is decreased *[see Drug Interactions (9)]*.

Special Populations

Comparison of the pharmacokinetics of d- and l-amphetamine after oral administration of MAS ER in children (6 to 12 years) and adolescent (13 to 17 years) ADHD patients and healthy adult volunteers indicates that body weight is the primary determinant of apparent differences in the pharmacokinetics of d- and l-amphetamine across the age range. Systemic exposure measured by area under the curve to infinity (AUC_{∞}) and maximum plasma concentration (C_{max}) decreased with increases in body weight, while oral volume of distribution (V_Z/F), oral clearance (CL/F), and elimination half-life ($t_{1/2}$) increased with increases in body weight.

Pediatric Patients
On a mg/kg weight basis, children eliminated amphetamine faster than adults. The elimination half-life ($t_{1/2}$) is approximately 1 hour shorter for d-amphetamine and 2 hours shorter for l-amphetamine in children than in adults. However, children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of MAS ER, which was attributed to the higher dose administered to children on a mg/kg body weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults.

Gender
Systemic exposure to amphetamine was 20% to 30% higher in women (N=20) than in men (N=20) due to the higher dose administered to women on a mg/kg body weight basis. When the exposure parameters (C_{max} and AUC) were normalized by dose (mg/kg), these differences diminished. Age and gender had no direct effect on the pharmacokinetics of d- and l-amphetamine.

Race
Formal pharmacokinetic studies for race have not been conducted. However, amphetamine pharmacokinetics appeared to be comparable among Caucasians (N=33), Blacks (N=8) and Hispanics (N=10).

Patients with Renal Impairment
The effect of renal impairment on *d*- and *l*-amphetamine after administration of MAS ER has not been studied. The impact of renal impairment on the disposition of amphetamine is expected to be similar between oral administration of lisdexamfetamine and MAS ER.

In a pharmacokinetic study of lisdexamfetamine in adult subjects with normal and impaired renal function, mean d-amphetamine clearance was reduced from 0.7 L/hr/kg in normal subjects to 0.4 L/hr/kg in subjects with severe renal impairment (GFR 15 to <30mL/min/1.73m^2). Dialysis did not significantly affect the clearance of *d*-amphetamine *[see Use in Specific Populations (10)]*.

14 NONCLINICAL TOXICOLOGY

14.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
No evidence of carcinogenicity was found in studies in which *d,l*-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day given to children, on a mg/m^2 basis.

Mutagenesis
Amphetamine, in the enantiomer ratio d- to l- ratio of 3:1, was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test *in vitro*. d,l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Impairment of Fertility
Amphetamine, in the enantiomer ratio d- to l- 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 (approximately 8 times the maximum recommended human dose of 20 mg/day given to adolescents, on a mg/m^2 basis).

14.2 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.

15 CLINICAL STUDIES

Pediatric Patients
A double-blind, randomized, placebo-controlled, parallel-group study was conducted in children aged 6 to 12 (N=584) who met DSM-IV® criteria for ADHD (either the combined type or the hyperactive-impulsive type). Patients were randomized to fixed-dose treatment groups receiving final doses of 10, 20, or 30 mg of MAS ER or placebo once daily in the morning for three weeks. Significant improvements in patient behavior, based upon teacher ratings of attention and hyperactivity, were observed for all MAS ER doses compared to patients who received placebo, for all three weeks, including the first week of treatment, when all MAS ER subjects were receiving a dose of 10 mg/day. Patients who received MAS ER showed behavioral improvements in both morning and afternoon assessments compared to patients on placebo.

In a classroom analogue study, patients (N=51) receiving fixed doses of 10 mg, 20 mg or 30 mg MAS ER demonstrated statistically significant improvements in teacher-rated behavior and performance measures, compared to patients treated with placebo.

A double-blind, randomized, multi-center, parallel-group, placebo-controlled study was conducted in adolescents aged 13 to 17 (N=327) who met DSM-IV® criteria for ADHD. The primary cohort of patients (n=287, weighing ≤75kg/165 lbs) was randomized to fixed-dose treatment groups and received four weeks of treatment. Patients were randomized to receive final doses of 10 mg, 20 mg, 30 mg, and 40 mg MAS ER or placebo once daily in the morning. Patients randomized to doses greater than 10 mg were titrated to their final doses by 10 mg each week. The secondary cohort consisted of 40 subjects weighing >75kg/165 lbs who were randomized to fixed-dose treatment groups receiving final doses of 50 mg and 60 mg MAS ER or placebo once daily in the morning for 4 weeks. The primary efficacy variable was the Attention Deficit Hyperactivity Disorder-Rating Scale IV (ADHD-RS-IV) total score for the primary cohort. The ADHD-RS-IV is an 18-item scale that measures the core symptoms of ADHD. Improvements in the primary cohort were statistically significantly greater in all four primary cohort active treatment groups (MAS ER10 mg, 20 mg, 30 mg, and 40 mg) compared with the placebo group. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

Adult Patients
A double-blind, randomized, placebo-controlled, parallel-group study was conducted in adults (N=255) who met DSM-IV® criteria for ADHD. Patients were randomized to fixed-dose treatment groups receiving final doses of 20, 40, or 60 mg of MAS ER or placebo once daily in the morning for four weeks. Significant improvements, measured with the Attention Deficit Hyperactivity Disorder-Rating Scale (ADHD-RS), an 18-item scale that measures the core symptoms of ADHD, were observed at endpoint for all MAS ER doses compared to patients who received placebo for all four weeks. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

16 HOW SUPPLIED/STORAGE AND HANDLING

Attent XR capsules are available as follows:

5 mg – #3 capsule with light blue opaque cap and orange opaque body printed with R and 3062 on the cap and body in black ink
10 mg – #3 capsule with light blue opaque cap and ivory opaque body printed with R and 3059 on the cap and body in black ink
15 mg – #2 capsule with ivory opaque cap and orange opaque body printed with R and 3063 on the cap and body in black ink
20 mg – #2 capsule with light blue opaque cap and light blue opaque body printed with R and 3060 on the cap and body in black ink
25 mg – #1 capsule with ivory opaque cap and ivory opaque body printed with R and 3064 on the cap and body in black ink
30 mg – #1 capsule with orange opaque cap and orange opaque body printed with R and 3061 on the cap and body in black ink

List of excipients

Excipients with known effect:
Sugar Spheres (sucrose and corn starch), Ammonio Methylacrylate copolymer, Talc, Hydroxypropyl cellulose, Triethyl citrate.

The capsule shells and printing ink contain:
5 mg: Gelatin, Titanium Dioxide, Yellow Iron Oxide, FD&C Blue # 1,Red Iron Oxide
10 mg: Gelatin, Titanium Dioxide, FD&C Blue # 1, D&C Yellow # 10,
15 mg: Gelatin, Titanium Dioxide, Yellow Iron Oxide, Red Iron Oxide, D&C Yellow # 10
20 mg: Gelatin, Titanium Dioxide, FD&C Blue # 1
25 mg: Gelatin, Titanium Dioxide, D&C Yellow # 10
30 mg: Gelatin, Titanium Dioxide, Yellow Iron Oxide, Red Iron Oxide

As well as: Shellac glaze, FD & C Red # 40 (E129), FD & C Blue # 2(E132), FD & C Blue # 1(E133), D & C Yellow # 10, Iron oxide black and Propylene Glycol

Shelf life

The expiry date of the product is indicated on the packaging materials.

Special precautions for storage

Store below 25°C.
The medicine can be used for up to 60 days after first opening of the bottle, but not after the expiry date.

Nature and contents of container

Plastic bottle of 30 capsules with a child-resistant closure.
Not all product strengths may be marketed

17 MANUFACTURER AND LICENSE HOLDER

Teva Israel Ltd.,
124 Dvora HaNevi'a St., Tel Aviv 6944020

18 REGISTRATION NUMBERS

Attent XR 5 mg registration No.: 170-89-35975
Attent XR 10 mg registration No.: 170-90-35994
Attent XR 15 mg registration No.: 170-91-35995
Attent XR 20 mg registration No.: 170-92-35996
Attent XR 25 mg registration No.: 170-93-35997
Attent XR 30 mg registration No.: 170-94-35998

להלן הבהרה לגבי כמות הכמוסות שניתן לנפק עבור התכשיר:
בהתאם לתקנות הרוקחים (ניפוקם והעברתם של סמים), תשמ"ג-1983, 3 (א) (5) והתוספת לתקנה זו, ניתן לנפק במרשם רופא מתאים כמות תרופה שלא תעלה על 40 מ"ג (בסיס) אמפטמין ליום.

לפיכך, בהתייחס לכמות בסיס האמפטמין בכמוסה, ניתן לנפק את סך הכמויות החודשיות המירביות של כמוסות אטנט XR כמפורט להלן:

	תכולת בסיס האמפטמין בכמוסה	**מספר כמוסות מירבי ליממה**	**מספר כמוסות מירבי בחודש**
אטנט XR 5 מ"ג	3.1 מ"ג	12	360
אטנט XR 10 מ"ג	6.3 מ"ג	6	180
אטנט XR 15 מ"ג	9.4 מ"ג	4	120
אטנט XR 20 מ"ג	12.6 מ"ג	3	90
אטנט XR 25 מ"ג	15.6 מ"ג	2	60
אטנט XR 30 מ"ג	18.8 מ"ג	2	60

ניפוק כמות העולה על 40 מ"ג ועד 100 מ"ג בסיס אמפטמין ליממה, דורש טופס מיוחד.

כלומר, עד מספר הכמוסות המפורט בטבלה בעמודה "מספר כמוסות מירבי בחודש", אין צורך בטופס מיוחד, מעבר למרשם הסמים לתכשיר.

The leaflet was revised in January 2025.