SUMMARY OF PRODUCT CHARACTERISTICS

Attent 10 mg, 20 mg & 30 mg
Tablets

1. NAME OF THE MEDICINAL PRODUCT

Attent 10 mg
Attent 20 mg
Attent 30 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A single entity amphetamine product combining the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d, l-amphetamine aspartate.

EACH TABLET CONTAINS	Attent 10 mg	Attent 20 mg	Attent 30 mg
Dextroamphetamine Saccharate	2.5 mg	5 mg	7.5 mg
Amphetamine Aspartate Monohydrate	2.5 mg	5 mg	7.5 mg
Dextroamphetamine Sulfate	2.5 mg	5 mg	7.5 mg
Amphetamine Sulfate	2.5 mg	5 mg	7.5 mg
Total amphetamine base equivalence	6.3 mg	12.6 mg	18.8 mg

Excipients with known effect:
Saccharin sodium, compressible sugar, Attent 20 mg and 30 mg tablets contain FD & C Yellow No. 6 Aluminium lake (sunset yellow FCF). See section 4.4 "excipients with known effect".
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets for oral administration.

ATTENT 10 mg:
Blue oval tablet, debossed with "b" over "972" between two horizontal lines on one side. On the other side, debossed with "1" and "0" on both sides of a bisect line [1 | 0] and between two horizontal lines.

ATTENT 20 mg:
Peach oval tablet, debossed with "b" over "973" between two horizontal lines on one side. On the other side, debossed with "2" and "0" on both sides of a bisect line [2 | 0] and betweentwo horizontal lines.

ATTENT 30 mg
Peach oval tablet, debossed with "b" over "974" between two horizontal lines on one side. On the other side, debossed with "3" and "0" on both sides of a bisect line [3 | 0] and between two horizontal lines.

Attent tablets can be divided into equal parts.

WARNING: ABUSE, MISUSE, AND ADDICTION

Attent tablets 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 tablets, can result in overdose and death (see OVERDOSE), and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing Attent tablets, 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 Attent tablets treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE **and** DRUG ABUSE AND DEPENDENCE**).**

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Attention Deficit Hyperactivity Disorder (ADHD) and Narcolepsy.

Attention Deficit Hyperactivity Disorder (ADHD)

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; Diagnostic and Statistical Manual of Mental Disorders, 4th edition, known as DSM-IV and published by the American Psychiatric Association) 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 child and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program:
ATTENT tablets 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 children with this syndrome. Stimulants are not intended for use in the child 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 ATTENT tablets for long-term use has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ATTENT tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

4.2 Posology and method of administration

Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted according to the therapeutic needs and response of the patient. Late evening doses should be avoided because of the resulting insomnia.

Attention Deficit Hyperactivity Disorder
Not recommended for children under 3 years of age.
In children from 3 to 5 years of age: as tablets of lower strength than 10 mg are required and are not registered in Israel, no dosage can be recommended.

Children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

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

Narcolepsy
Usual dose 5 mg to 60 mg per day in divided doses, depending on the individual patient response.

Narcolepsy seldom occurs in children under 12 years of age; however, when it does, dextroamphetamine sulfate may be used. The suggested initial dose for patients aged 6 to 12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

4.3 Contraindications

- In patients known to be hypersensitive to any of the active substances or to any of the excipients listed in section 6.1.
  Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other amphetamine products (see UNDESIRABLE EFFECTS).

- Patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs (including MAIOs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crises (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE and INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION).

4.4 Special warnings and precautions for use

Abuse, Misuse, and Addiction

Attent tablets have a high potential for abuse and misuse. The use of Attent tablets exposes individuals to the risks of abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Attent tablets can be diverted for non-medical use into illicit channels or distribution (see DRUG ABUSE and DEPENDENCE). Misuse and abuse of CNS stimulants, including Attent tablets can result in overdose and death (see OVERDOSE), and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing Attent tablets, 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 tablets in a safe place, preferably locked, and instruct patients to not give Attent tablets to anyone else. Throughout Attent tablets treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

Risk to Patients with Serious Cardiovascular Events

Sudden death has been reported in patients with structural cardiac abnormalities or other serious cardiac disease who were treated with CNS stimulant treatment at the recommended ADHD dosages.

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

Increased Blood Pressure and Heart Rate

CNS stimulants cause an increase in blood pressure (mean increase about 2 to 4 mmHg) and heart rate (mean increase about 3 to 6 bpm). Some patients may have larger increases. Monitor all Attent tablets-treated patients for potential tachycardia and hypertension.

Psychiatric Adverse Events

Exacerbation of Pre-Existing Psychosis

CNS 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 Disorder

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

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without 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 with 0% of placebo-treated patients. If such symptoms occur, consider discontinuing Attent tablets.

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

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Seizures

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

Peripheral Vasculopathy, Including Raynaud's Phenomenon
Stimulants, including ATTENT (Mixed Amphetamine Salts), used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in postmarketing reports and at the therapeutic doses 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 Attent tablets treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for Attent tablet-treated patients who develop signs or symptoms of peripheral vasculopathy.

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]. The coadministration with cytochrome P450 (CYP2D6) inhibitors increase the risk with increased exposure to ATTENT tablets. In these situations, consider an alternative non-serotonergic drug or an alternative drug that does not inhibit CYP2D6 [see Drug Interactions].

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 tablets with MAOI drugs is contraindicated [see Contraindications].

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

Motor and Verbal Tics, and Worsening of Tourette's Syndrome
CNS stimulants, including amphetamine sulfate, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Before initiating Attent tablets, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome with Attent tablets, and discontinue treatment if clinically appropriate
Other Precautions

Excipients with Known Effect

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".
This medicine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
Attent 20 mg and 30 mg tablets contain FD & C Yellow No. 6 Aluminium lake that may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

MAO Inhibitors
Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophtalmological complications, eclampsia, pulmonary edema and renal failure. Do not administer ATTENT tablets concomitantly or within 14 days after discontinuation MAOI (see Contraindications and Warnings).

Serotonergic Drugs
The concomitant use of ATTENT tablets and serotonergic drugs increases the risk of serotonin syndrome. Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome, particularly during ATTENT tablets initiation or dosage increase. If serotonin syndrome occurs, discontinue ATTENT tablets and the concomitant serotonergic drug(s) [see WARNINGS and PRECAUTIONS].

CYP2D6 Inhibitors
The concomitant use of ATTENT tablets and CYP2D6 inhibitors may increase the exposure of ATTENT tablets compared to the use of the drug alone and increase the risk of serotonin syndrome. Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during ATTENT tablets initiation and after a dosage increase. If serotonin syndrome occurs, discontinue ATTENT tablets and the CYP2D6 inhibitor [see WARNINGS, OVERDOSAGE].

Acidifying Agents
Lower blood levels and efficacy of amphetamines. Increase dose based on clinical response. Examples of acidifying agents include gastrointestinal acidifying agents and urinary acidifying.

Adrenergic Blockers
Adrenergic blockers are inhibited by amphetamines.

Alkalinizing Agents
Increase blood levels and potentiate the action of amphetamine. Co-administration of ATTENT tablets and gastrointestinal alkalizing agents should be avoided. Examples of alkalizing agents include gastrointestinal alkalizing agents and urinary alkalinizing agents.

Tricyclic Antidepressants
Amphetamines 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. Monitor frequently and adjust or use alternative therapy based on clinical response.

Antihistamines
Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives
Amphetamines may antagonize the hypotensive effects of antihypertensives.

Chlorpromazine
Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.

Ethosuximide
Amphetamines may delay intestinal absorption of ethosuximide.

Haloperidol
Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.

Lithium Carbonate
The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.

Meperidine (Pethidine)
Amphetamines potentiate the analgesic effect of meperidine.

Methenamine Therapy
Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.

Norepinephrine
Amphetamines enhance the adrenergic effect of norepinephrine.

Phenobarbital
Amphetamine may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

Phenytoin
Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

Propoxyphene
In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

Proton Pump Inhibitors (PPIs)
Time to maximum concentration (T_{max}) of amphetamine is decreased compared to when administered alone. Monitor patients for changes in clinical effect and adjust therapy based on clinical response. An example of proton pump inhibitor is omeprazole.

Veratrum Alkaloids
Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

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.

4.6 Fertility, pregnancy and lactation

Fertility
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 [child] on a mg/m^2 body surface area basis.

Amphetamine, in the enantiomer ratio present in Attent tablets (immediate-release) (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.

Amphetamine, in the enantiomer ratio present in ATTENT tablets (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 5 times the maximum recommended human dose of 30 mg/day on a mg/m2 body surface area basis).

Pregnancy

Teratogenic effects

Amphetamine, in the enantiomer ratio present in this product (d- to l- ratio of 3:1), had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 1.5 and 8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m^2 body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 times that of a human dose of 30 mg/day [child] on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

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

There are no adequate and well-controlled studies in pregnant women. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

Lactation

Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

Pediatric Use

Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age with Attention Deficit Hyperactivity Disorder.

Geriatric Use

ATTENT tablets have not been studied in the geriatric population.

4.7 Effects on ability to drive and use machines

This product may affect your or your child's ability to drive or do other dangerous activities.

4.8 Undesirable effects

Cardiovascular

Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System
Psychotic episodes at recommended doses, overstimulation, restlessness, irritability, euphoria, dyskinesia, dysphoria, depression, aggression, anger, logorrhea, dermatillomania, tremor, motor and verbal tics,.

Eye Disorders
Vision blurred, mydriasis.

Gastrointestinal
Dryness of the mouth, unpleasant taste, diarrhea, constipation, intestinal ischemia and other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.

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

Endocrine
Impotence, changes in libido, frequent or prolonged erections

Skin
Alopecia

Musculoskeletal
Rhabdomyolysis

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

DRUG ABUSE AND DEPENDENCE
Abuse
Attent tablets have a high potential for abuse and misuse which can lead to the development of a substance use disorder, including addiction. Attent tablets 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 amphetamines 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 Attent tablets, can result in overdose and death [see **OVERDOSE**], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Dependence
Physical Dependence
Attent tablets may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal signs and symptoms after abrupt discontinuation or dose reduction following prolonged use of CNS stimulants including Attent tablets include dysphoric mood; depression; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

Tolerance
Attent tablets 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).

4.9 Overdose
Symptoms
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 40°C) and rhabdomyolysis may develop.

Treatment
Consider the possibility of multiple drug ingestion. D-amphetamine is not dialyzable. Consult with a certified poison control center for up to date guidance and advice.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mixed Salts Amphetamines

ATC Code: N06BA01

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

5.2 Pharmacokinetic properties
ATTENT (Amphetamine Mixed Salts) tablets contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of a single dose 10 or 30 mg of the product to healthy volunteers under fasted conditions, peak plasma concentrations occurred approximately 3 hours post-dose for both d-amphetamine and l-amphetamine. The mean

elimination half-life ($t_{1/2}$) for d-amphetamine was shorter than the $t_{1/2}$ of the l-isomer (9.77-11 hours vs. 11.5-13.8 hours). The PK parameters (C_{max}, AUC_{0-inf}) of d-and l-amphetamine increased approximately three-fold from 10 mg to 30 mg indicating dose-proportional pharmacokinetics.

The effect of food on the bioavailability of Amphetamine Mixed Salts tablets has not been studied.

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%-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.

5.3 Preclinical safety data

Carcinogenesis/Mutagenesis and Impairment of Fertility
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 [child] on a mg/m^2 body surface area basis.

Amphetamine, in the enantiomer ratio present in this product (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.

Amphetamine, in the enantiomer ratio present in this product(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 5 times the maximum recommended human dose of 30 mg/day on a mg/m^2 body surface area basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide, compressible sugar (sucrose and maltodextrin), corn starch, magnesium stearate, microcrystalline cellulose and saccharin sodium.

Each tablets also contains	10 mg	20 mg	30 mg
FD&C Blue No. 1 Aluminium Lake	v	--	--
FD&C Yellow No. 6 Aluminium Lake (sunset yellow FCF)	--	v	v
Sodium content per tablet (approximate)	0.45 mg	0.45 mg	0.67 mg
Sucrose content per tablet (approximate)	98 mg	93 mg	140 mg

6.2 Special precautions for storage

Store below 25°C and protect from light.
The medicine can be used for up to 90 days after first opening of the bottle, but not after the expiry date.

6.3 Nature and contents of container

Each plastic bottle of 30 tablets contains a desiccant.

להלן הבהרה לגבי כמות הטבליות שניתן לנפק עבור התכשיר אטנט:
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 בטבליה, ניתן לנפק את סך הכמויות החודשיות המירביות של טבליות אטנט כמפורט להלן:

	תכולת בסיס האמפטמין בטבליה	מספר טבליות מירבי ליממה	מספר טבליות מירבי בחודש
אטנט 10 מ"ג	6.3 מ"ג	6	180
אטנט 20 מ"ג	12.6 מ"ג	3	90
אטנט 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 הטבליות המפורט בטבלה בעמודה "מספר טבליות מירבי בחודש", אין צורך בטופס מיוחד, מעבר למרשם הסמים לתכשיר.

7. Manufacturer and License Holder

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

8. REGISTRATION NUMBERS

Attent 10 mg registration No.: 154-13-34222
Attent 20 mg registration No.: 154-14-34224
Attent 30 mg registration No.: 154-15-34225

This leaflet was revised in August 2024 according to Ministry of Health guidelines.