Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tentin 5mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg dexamfetamine sulphate.

Excipient with known effect:

Isomalt (E953) 147.5 mg per tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

White, round, cloverleaf-shaped tablets of 8.4 mm diameterwith a notched, cross-scored line on the top side and a cross-scored line embossed with “S” on each quarter on the rear side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Dexamfetamine is indicated as part of a comprehensive treatment programme for attention-aeficit/hyperactivity disorder (ADHD) in children and adolescents aged 6 to 17 years when response to previous methylphenidate treatment is considered clinically inadequate. A comprehensive treatment programme typically includes psychological, educational and social measures.

Diagnosis should be made according to DSM-5 criteria or the guidelines in ICD-10 and should be based on a comprehensive multidisciplinary evaluation of the patient.

Dexamfetamine is not indicated in all children with ADHD and the decision to use dexamfetamine must be based on a very thorough assessment of the severity and chronicity of the child’s symptoms in relation to the child’s age and potential for abuse, misuse or diversion.

Treatment should be under the supervision of a specialist in childhood and/or adolescent behavioural disorders.

4.2 Posology and method of administration

Posology

Treatment must be under the supervision of a specialist in childhood and/or adolescent behaviour disorders.

Careful dose titration is necessary at the start of treatment with dexamfetamine. Dose titration should be started at the lowest possible dose.

The recommended starting daily dose is 5 mg once or twice daily (e.g. at breakfast and lunch), increasing if necessary by weekly increments of 5 mg in the daily dose according to tolerability and degree of efficacy observed.

In the treatment of hyperkinetic disorders / ADHD, the times at which the doses of Tentin 5 mg are administered should be selected to provide the best effect when it is most needed to combat school and social behavioural difficulties. Normally the first increasing dose is given in the morning. Tentin 5 mg should not be taken too late after lunch time to avoid disturbances of sleep.

The regimen that achieves satisfactory symptom control with the lowest total daily dose should be employed.

The maximum daily dose in children and adolescent usually is 20 mg, although doses of 40 mg may in rare cases be necessary for optimum titration

Long-term use

Long-term usefulness of dexamfetamine for extended periods (over 12 months) in children and adolescents with ADHD should be periodically re-evaluated for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that dexamfetamine is de-challenged at least once yearly to assess the child's condition (preferably during times of school holidays). Improvement may be sustained when the medicinal product is either temporarily or permanently discontinued.

Dose reduction and discontinuation

Treatment must be stopped if the symptoms do not improve after appropriate dosage adjustment over a one-month period. If paradoxical aggravation of symptoms or other serious adverse events occur, the dosage should be reduced or discontinued.

Special populations

Children under 6 years of age
The safety and efficacy of Tentin 5 mg in children aged 0 to 6 years has not been established.
Therefore Tentin 5 mg should not be used in children under the age of 6 years.

Use in Adults
Tentin 5 mg is not licensed for use in adults. The safety and efficacy of dexamfetamine in adults have not been established.

Elderly
Tentin 5 mgshould not be used in the elderly. Safety and efficacy of dexamfetamine has not been established in this age group.

Patients with renal or hepatic insufficiency
There is no experience with the use of dexamfetamine in patients with renal or hepatic insufficiency.
Thus, dexamfetamine should be used with special caution in this patient group by taking care of titration and dosage

Method of administration

Oral use

The tablets may be swallowed whole with the aid of liquids, or alternatively, in cases of swallowing problems the tablets can be divided.

The tablet score lines enable division of the tablet into four parts. For division, the tablet is placed onto a hard surface with its cross- scored, convex side downwards and is then pushed carefully with the index finger at the centre of its top side. The tablet then breaks into four parts. Drinking some fluids, e.g. water, should follow the intake of the divided tablets.

The effect of food on the absorption of dexamfetamine from Tentin 5 mgtablets has not been studied; therefore, a possible effect of food on absorption cannot be excluded. Therefore, it is recommended that Tentin 5 mg tablets should be taken in a standardised manner in relation to the timing of meals, i.e. that doses should be given at the same times, relative to the time of meals, on each day, preferably with or immediately after meals.

4.3 Contraindications

- Known hypersensitivity to the active substance or any of the excipients listed in section 6.1
- Known hypersensitivity to sympathomimetic amines
- Glaucoma
- Phaeochromocytoma
- Symptomatic cardiovascular disease, structural cardiac abnormalities and/or moderate or severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels)
- Advanced arteriosclerosis
- Concomitant use of monoamine oxidase inhibitors (MAOI) or within 14 days of MAOI treatment
- Hyperthyroidism or thyrotoxicosis.
- Severe depression, anorexia nervosa/anorexic disorders, suicidal ideation, hyperexcitability, psychotic symptoms, severe and episodic (Type I) Bipolar (affective) Disorder (that is not well-controlled), schizophrenia, psychopathic/borderline personality disorder
- Gilles de la Tourette syndrome or similar dystonias.
- Cerebrovascular disorders (cerebral aneurysm, vascular abnormalities including vasculitis or stroke)
- Porphyria
- History of drug abuse or alcohol abuse

4.4 Special warnings and precautions for use

Precautions to be taken before handling or administering the medicinal product

Pre-treatment screening:

Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate. A comprehensive history should document concomitant medications, past and present co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death and accurate recording of pre-treatment height and weight on a growth chart (see sections 4.3 and 4.4)

Ongoing monitoring

- Growth, psychiatric and cardiovascular status should be continuously monitored (see also Section 4.4).
- Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months;
- Height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart;

- Development of de novo or worsening of pre-existing psychiatric disorders, including depression and aggressive behaviour, should be monitored at every adjustment of dose and then at least every 6 months and at every visit.
- Patients should be monitored for the risk of diversion, misuse, and abuse of dexamfetamin

Long-term use (more than 12 months) in children and adolescents

The safety and efficacy of long-term use of dexamfetamine has not been systematically evaluated in controlled trials. Dexamfetamine treatment should not be and does not need to be indefinite. Dexamfetamine treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance in sections 4.2 and 4.4 for cardiovascular status, growth, appetite, and development of de novo or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below, and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal, and excessive perseveration.

The physician who elects to use dexamfetamine for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long-term usefulness of the medicinal product for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that dexamfetamine is de-challenged at least once yearly to assess the child's condition (preferably during times of school holidays). Improvement may be sustained when the medicinal product is either temporarily or permanently discontinued.

Cardiovascular status

Patients who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Patients who develop symptoms such as palpitations, exceptional chest pain, unexplained syncope, dyspnoea, or other symptoms suggestive of cardiac disease during dexamfetamine treatment should undergo a prompt specialist cardiac evaluation.

Cardiovascular status should be carefully monitored. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months.

Treatment with stimulants in general may lead to a minor increase in blood pressure (approx. 2-4 mm Hg) as well as an increase in heart rate (approx. 3-6 beats/minute). In few patients, these values may be higher.

The short- and long-term clinical consequences of these cardiovascular effects in children and adolescents are not known, but the possibility of clinical complications

cannot be excluded as a result of the effects observed in the clinical trial data. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. See section 4.3 for conditions in which dexamfetamine treatment in contraindicated.

The use of dexamfetamine is contraindicated in certain pre-existing cardiovascular disorders unless specialist paediatric cardiac advice has been obtained (see section 4.3).

Sudden death and pre-existing cardiac structural abnormalities or other serious cardiac disorders

Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children, some of whom had cardiac structural abnormalities or other serious heart problems. Although some serious heart problems alone may carry an increased risk of sudden death, stimulant products are not recommended in children or adolescents with known cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the onset of sympathomimetic effects of a stimulant medicine (see section 4.3).

Cardiovascular events

Misuse of stimulants of the central nervous system may be associated with sudden death and other serious cardiovascular adverse events.

Cases of cardiomyopathy have been observed with chronic use of amfetamine.

Cerebrovascular disorders

See section 4.3 for cerebrovascular conditions in which dexamfetamine treatment is contraindicated. Patients with additional risk factors (such as a history of cardiovascular disease or concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with dexamfetamine.

Cerebral vasculitis appears to be a very rare idiosyncratic reaction to dexamfetamine exposure. There is little evidence to suggest that patients at higher risk can be identified and the initial onset of symptoms may be the first indication of an underlying clinical problem. Early diagnosis, based on a high index of suspicion, may allow the prompt withdrawal of dexamfetamine and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during dexamfetamine therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language, or memory. Treatment with dexamfetamine is not contraindicated in patients with hemiplegic cerebral palsy.

Psychiatric disorders

Comorbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, dexamfetamine should not be given unless the benefits outweigh the risks to the patient.

Development or worsening of psychiatric disorders should be monitored at every adjustment of dose, then at least every 6 months, and at every visit; discontinuation of treatment may be appropriate.

Exacerbation of pre-existing psychotic or manic symptoms

In psychotic patients, administration of dexamfetamine may exacerbate symptoms of behavioural disturbance and thought disorder.

Emergence of new psychotic or manic symptoms

Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in children and adolescents without prior history of psychotic illness or mania can be caused by dexamfetamine at usual doses.

A pooled analysis of various short-term, placebo-controlled studies revealed that such symptoms occurred in approx. 0.1% of patients (4 out of 3,482) who were treated with dexamfetamine or amfetamine for several weeks, whereas none of the patients of the placebo group were affected by these symptoms.

If manic or psychotic symptoms occur, consideration should be given to a possible causal role for dexamfetamine, and discontinuation of treatment may be appropriate.

Aggressive or hostile behaviour

The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Patients treated with dexamfetamine should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and at every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes.

Suicidal ideation

Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Consideration should be given to the exacerbation of an underlying psychiatric condition and to a possible causal role of dexamfetamine treatment. Treatment of an underlying psychiatric condition may be necessary and consideration should be given to a possible discontinuation of dexamfetamine.

Tics

Dexamfetamine is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede the use of dexamfetamine. Patients should be regularly monitored for the emergence or worsening of tics during treatment with dexamfetamine. Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.

Anxiety, agitation, or tension

Dexamfetamine is associated with the worsening of pre-existing anxiety, agitation, or tension. Clinical evaluation for anxiety, agitation or tension should precede use of dexamfetamine and patients should be regularly monitored for the emergence or worsening of these symptoms during treatment, at every adjustment of dose and then at least every 6 month or at every visit.

Forms of bipolar disorder

Particular care should be taken in using dexamfetamine to treat ADHD in patients with comorbid bipolar disorder (including untreated type I bipolar disorder or other forms of bipolar disorder) because of concerns for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with dexamfetamine, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. Such a screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Close ongoing monitoring is essential in these patients (see above 'Psychiatric disorders' and section 4.2). Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.

Growth

Moderately reduced weight gain and growth retardation have been reported with the long-term use of dexamfetamine in children.

The effects of dexamfetamine on final height and final weight are currently unknown and being studied.

Growth should be monitored during dexamfetamine treatment: height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

As a reduction in appetite may occur during treatment with dexamfetamine, the medicinal product may only be administered with special caution to patients with Anorexia nervosa.

Seizures

Dexamfetamine should be used with caution in patients with epilepsy. Dexamfetamine may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in the absence of seizures, and rarely in patients without a history of convulsions and no EEG abnormalities. If seizure frequency increases or new-onset seizures occur, dexamfetamine should be discontinued.

Abuse, misuse, and diversion

Patients should be carefully monitored for the risk of diversion, misuse, and abuse of dexamfetamine.

The risk is generally greater for short acting stimulants than for corresponding long-acting products (see section 4.1).

Dexamfetamine should not be used in patients with known drug or alcohol dependency because of a potential for abuse, misuse, or diversion.

Chronic abuse of dexamfetamine can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially in response to parenteral abuse.

Signs of chronic amfetamine intoxication include severe dermatoses, pronounced sleeplessness, confusion, hyperactivity, and personality changes. The most severe

sign of chronic amfetamine intoxication is a psychosis which in most cases can hardly be clinically distinguished from schizophrenia. However, such a psychosis rarely occurs after oral ingestion of amfetamines. There have also been reports of intracerebral bleeding. Serious cardiovascular events observed in association with amfetamine misuse were sudden death, cardiomyopathy, and myocardial infarction.
Patient age, the presence of risk factors for substance use disorder (such as comorbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should all be taken into account when deciding on a course of treatment for ADHD. Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because such patients may increase the dosage on their own initiative.
For some high-risk substance abuse patients, dexamfetamine or other stimulants may not be suitable. This may also be true for other stimulants and therefore, non-stimulant treatment should be considered.
Withdrawal
Careful supervision is required during withdrawal of the medicinal product, since this may unmask depression as well as chronic over-activity. Some patients may require long-term follow up.
Similarly, careful supervision is required during withdrawal from abusive use since severe depression may occur.
Abrupt withdrawal after a prolonged period of intake of high doses of dexamfetamine may cause extreme fatigue as well as changes in the EEG during sleep.
Fatigue
Dexamfetamine should not be used for the prevention or treatment of normal fatigue states.
Drug screening
This product contains dexamfetamine which may induce a positive laboratory test for amfetamines, particularly with an immunoassay screening test.
Athletes must be aware that this medicinal product may cause a positive reaction to'anti-doping' tests.
Renal or hepatic insufficiency
There is no experience with the use of dexamfetamine in patients with renal or hepatic insufficiency. In those patients peak plasma levels could be higher and elimination could be prolonged. Thus, dexamfetamine should be used with special caution in this patient group by taking care of titration and dosage.
Haematological effects
The long-term safety of treatment with dexamfetamine is not fully known. In the event of leukopenia, thrombocytopenia, anaemia, or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.
Excipient: isomalt

This medicinal product contains isomalt. Due to the presence of isomalt in the formulation, patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Because of possible hypertensive crisis, dexamfetamine is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors (see section 4.3).

It is not known whether dexamfetamine may inhibit or induce cytochrome P450 (CYP) enzymes. Co-administration of CYP substrates with narrow therapeutic index should therefore be made with caution.

It is not known to which degree dexamfetamine metabolism is dependent on CYP enzymes. Co-administration of potent inhibitors or inducers of CYP enzymes should be made with caution.

Agents that lower blood levels of amphetamines

Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower the absorption of amfetamines.

Agents that increase blood levels of amphetamines

Urinary acidifying agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amfetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amfetamines.

Gastrointestinal alkalinizing agents (sodium bicarbonate, etc**.**) increase the absorption of amfetamines. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amfetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amfetamines.

Concomitant administration of clonidine and dexamfetamine may result in an increased duration of the action of dexamfetamine.

Agents whose effects may be reduced by amfetamines

Dexamfetamine may counteract the sedative effect of antihistamines.

Dexamfetamine may inhibit the antihypertensive action of guanethidine or clonidine. Concomitant use of beta-blockers may lead to severe hypertonia, as the therapeutic action of these agents may be inhibited by dexamfetamine.

Depressant effects of opiates, e.g. respiratory depression, may be decreased by dexamfetamine.

Agents whose effects may be increased by amphetamines

Halogenated narcotics**:** There is a risk of sudden blood pressure increase during surgery. If surgery is planned, dexamfetamine treatment should not be used on the day of surgery.

Concomitant use of tricyclic antidepressants may increase the risk of cardiovascular adverse events.
Because of a possible increase in blood pressure, special caution is advised if Tentin 5 mg is administered to patients being treated with vasopressors (see also sections on cardiovascular and cerebrovascular conditions in section 4.4).

Dexamfetamine may enhance the adrenergic effect of noradrenaline.

Dexamfetamine may potentiate the analgesic effects of meperidine.

The analgesic action of morphine may be potentiated by the concomitant use of dexamfetamine,

Agents that may increase the effects of amphetamines

There are reports indicating that dexamfetamine may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, phenytoin, and primidone) and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with dexamfetamine, it may be necessary to adjust the dosage of these medicinal products already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Disulfiram may inhibit the metabolism and excretion of dexamfetamine.

Agents that may reduce the effects of amphetamines

Adrenergic blockers (e.g. propranolol), lithium, and α-methyltyrosine may attenuate the effects of dexamfetamine.

Concomitant use of haloperido**l** may inhibit the central stimulant effects of dexamfetamine. Acute dystonia has been noted with concurrent administration of haloperidol.

The absorption of anticonvulsants (e.g. phenobarbital, phenytoin, primidone, and ethosuximide) may be delayed by dexamfetamine.

Use with alcohol

Alcohol may exacerbate the CNS adverse reactions of psychoactive medicinal products, including dexamfetamine. It is therefore advisable for patients to abstain from alcohol during treatment.

Phenothiazines, e.g. chlorpromazine block dopamine receptors, thus inhibiting the central stimulant effects of amfetamines, and can be used to treat amfetamine poisoning.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of dexamfetamine in pregnant women.

Children of mothers who are dependent on amfetamine have been shown to beat an increased risk of premature birth and reduced birth weight.

Moreover, these children may develop withdrawal symptoms like dysphoria, including hyperexcitability and pronounced exhaustion.

Results of studies in animals suggest that high doses ofdexamfetamine may elicit reproductive toxicity (see section 5.3). The use of Tentin 5 mgduring pregnancy is not recommended. Women of childbearing age should discontinue the use of Tentin 5 mg when intending to become pregnant.

Breastfeeding

Dexamfetamine is excreted in human milk. A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Tentin 5 mgtherapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Dexamfetamine can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision. It may have a moderate influence on the ability to drive and use machines. Patients should be warned of

these possible effects and advised that if affected, they should avoid potentially hazardous activities such as driving or operating machinery.

4.8 Undesirable effects

Information on the frequency of these effects was obtained from published clinical studies and meta-analyses as well as the MHRA safety information.

Side-effect assessment is based on the following categories**:**

very common (≥ 1/10)
common (≥ 1/100 to < 1/10)
uncommon (≥ 1/1,000 to <1/100)
rare (≥ 1/10,000 to <1/1,000)
very rare (<1/10,000)
not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Very rare: Anaemia, leukopenia, thrombocytopenia, thrombocytopenic purpura

Cardiac disorders
Common: Arrhythmia, palpitations, tachycardia
Rare: Angina pectoris
Very rare: Cardiac arrest
Not known: Cardiomyopathy, myocardial infarction

Congenital, familial and genetic disorders
Very rare: Tourette's syndrome
Eye disorders
Rare: Difficulties in visual accommodation, blurred vision, mydriasis

Gastrointestinal disorders
Common: Abdominal pain and cramps, nausea, vomiting, dry mouth
These effects usually occur at the beginning of treatment and may be alleviated by concomitant food intake.
Not known: Ischaemic colitis, diarrhoea

General disorders and administration site conditions
Not known: Chest pain, hyperpyrexia, fatigue, sudden death (see section 4.4)

Hepatobiliary disorders
Very rare: Abnormal liver function ranging from hepatic enzyme elevations to hepatic coma

Immune system disorders
Not known hypersensitivity including angioedema and anaphylaxis

Investigations
Common: Changes in blood pressure and heart rate (usually increases)

Metabolism and nutrition disorders
Very common: Decreased appetite, reduced weight gain and weight loss during prolonged use in children
Not known: Acidosis

Musculoskeletal and connective tissue disorders
Common: Arthralgia
Rare: growth retardation during prolonged use in children
Very rare: Muscle cramps
Not known: Rhabdomyolysis

Nervous system disorders
Common: Vertigo, dyskinesia, headache, hyperactivity
Rare: Fatigue
Very rare: Convulsions, choreoathetoid movements, intracranial haemorrhage
Not known: Ataxia, dizziness, dysgeusia, concentration difficulties, hyperreflexia, stroke, tremor

Very rarely, cases of neuroleptic malignant syndrome (NMS) were observed. However, these reports were poorly documented and in most cases, patients were also receiving other medicinal products. Thus, the role of dexamfetamine in the development of NMS is unclear.

Psychiatric disorders
Very common: Insomnia, nervousness
Common: Abnormal behaviour, aggression, excitation, anorexia, anxiety, depression, irritability
Very rare: Hallucinations, psychosis / psychotic reactions, suicidal behaviour (including completed suicide), tics, worsening of pre-existing tics
Not known: Confusion, dependence, dysphoria, emotional lability, euphoria, impaired cognitive test performance, altered libido, night terrors, obsessive-compulsive behaviour, panic states, paranoia, restlessness

Renal and urinary disorders
Not known: Renal damage

Reproductive system and breast disorders
Not known: Impotence

Skin and subcutaneous tissue disorders
Rare: Rash, urticaria
Very rare: Erythema multiforme, exfoliative dermatitis, fixed drug eruption
Not known: Sweating, alopecia

Vascular disorders
Very rare: Cerebral vasculitis and/or occlusion
Not known: Cardiovascular collapse, Raynaud's phenomenon

A toxic hypermetabolic state, characterised by transient hyperactivity, hyperpyrexia, acidosis, and death due to cardiovascular collapse have been reported.

Cessation of, or reduction in amfetamine use that has been heavy and prolonged can result in withdrawal symptoms. Symptoms include dysphoric mood, fatigue, vivid and unpleasant dreams, insomnia or hypersomnia, increased appetite, psychomotor retardation or agitation, anhedonia, and drug craving.

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. Healthcare professionals are asked to report any suspected adverse reactions via:
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

Signs and symptoms

Acute overdose, mainly due to overstimulation of the central and sympathetic nervous systems, may result in vomiting, agitation, aggression, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, mydriasis, dryness of mucous membranes, flushing, headache, hyperpyrexia, chest pain, tachycardia, palpitations, cardiac arrhythmias, hypertension, respiratory depression, coma, circulatory collapse, and death.

Individual patient response may vary widely and toxic manifestations may occur with quite small overdoses.

Treatment

There is no specific antidote to dexamfetamine overdose. Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. If the signs and symptoms are not too severe and the patient is conscious, gastric contents may be evacuated by induction of vomiting when the medicinal product has been taken less than one hour before.Other measures to detoxify the gut include administration of activated charcoal and a cathartic.

Excessive stimulation or convulsions may be treated with benzodiazepines.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics; psychostimulants, agents used for ADHD and nootropics; centrally acting sympathomimetics

ATC Code: N06BA02

Mechanism of action

Dexamfetamine is a sympathomimetic amine with a central stimulant and anorectic activity.

Pharmacodynamic effects

Peripheral actions include elevations of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. Neither there is specific evidence that clearly establishes the mechanism whereby amfetamines produce mental and behavioural effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

5.2 Pharmacokinetic properties

Absorption

Dexamfetamine is highly lipophilic and rapidly absorbed from the gastrointestinal tract. The pharmacokinetics of the tablets was measured in 18 healthy subjects. Following the administration of one 5-mg tablet of Tentin 5 mg tablets, average

maximal plasma concentrations (C_{max}) of 11.5 ng/mL were achieved at approximately 1.5 hours.

Distribution

Following oral intake, amfetamines are rapidly distributed to major organ systems. Amfetamines are highly liposoluble and can cross the blood-brain barrier. Concentrations reached in the central nervous system may be 8 times higher than plasma levels. The plasma binding of amfetamine averages between 15 and 34%.

Biotransformation

The biotransformation of amfetamine takes place in the liver and mainly comprises hydroxylation and conjugation with glucuronic acid leading to more hydrophilic components which can be more easily eliminated. Smaller amounts of amfetamine are converted to norephedrine by oxidation. Hydroxylation produces an active metabolite (O-hydroxynorephedrine) which acts as a false neurotransmitter and may account for some drug effects, especially in chronic users.

Elimination

Amfetamine is primarily excreted in the urine; however, tubular reabsorption is relatively high due to its lipophilic properties. The elimination of amfetamine is pH-dependent, i.e. at low pH about 80% of the amfetamine may be eliminated in the unaltered form within 24 hours; in alkaline urine, there are only 2–3% of the amfetamine which will be eliminated as free amfetamine. The extent of bioavailability of the tablets was measured in 18 healthy subjects. The average plasma half-life ($t_{1/2}$) was 10.2 hours.

5.3 Preclinical safety data

Animal studies on general toxicity, safety pharmacology, genotoxicity and carcinogenicity of dexamfetamine did not reveal any adverse effects not already known in humans.

In studies on the reproductive toxicity of dexamfetamine in mice an increased risk of malformations was observed, but only at doses 41 times the human dose. In rats treated with a dose corresponding to 12.5 times the human dose and rabbits treated with doses of dexamfetamine corresponding to up to 7 times the human dose no embryotoxic effects were observed.

Behavioural studies in rodents revealed developmental delay, behavioural sensitization as well as increased motor activity in offspring after prenatal exposures to dexamfetamine at dose levels comparable to human therapeutic dose levels. The clinical relevance of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Isomalt (E953)
Crospovidone
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30 °C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Boxes containing 20, 30, 50, or 100 tablets in PVC/PE/PVdC clear blisters heat sealed to aluminium foil

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

MEDICE Arzneimittel Pütter GmbH & Co KG
Kuhloweg 37
58638 Iserlohn
Germany

8 MARKETING AUTHORISATION NUMBER

PA1555/003/001

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