Part VI: Summary of the risk management plan

Summary of risk management plan for ATTENTIN®/AMFEXA®/TENTIN® 5 mg, 10 mg, 20 mg (dexamfetamine sulfate)

This is a summary of the risk management plan (RMP) for ATTENTIN®/AMFEXA®/TENTIN® 5 mg, 10 mg, and 20 mg (hereinafter referred to as ATTENTIN®/AMFEXA®/TENTIN®). The RMP details important risks of ATTENTIN®/AMFEXA®/TENTIN®, how these risks can be minimised, and how more information will be obtained about ATTENTIN®/AMFEXA®/TENTIN®'s risks and uncertainties (missing information).

ATTENTIN®/AMFEXA®/TENTIN®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ATTENTIN®/AMFEXA®/TENTIN® should be used.

Important new concerns or changes to the current ones will be included in updates of the RMP for ATTENTIN®/AMFEXA®/TENTIN®.

I. The medicine and what it is used for

ATTENTIN®/AMFEXA®/TENTIN® is authorised as part of a comprehensive treatment programme for attention-deficit/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 (see SmPC for the full indication). It contains dexamfetamine sulfate as the active substance and it is given by oral route (tablet).

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.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of ATTENTIN®/AMFEXA®/TENTIN®, together with measures to minimise such risks and the proposed studies for learning more about ATTENTIN®/AMFEXA®/TENTIN®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of ATTENTIN®/AMFEXA®/TENTIN®, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of ATTENTIN®/AMFEXA®/TENTIN® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of ATTENTIN®/AMFEXA®/TENTIN® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ATTENTIN®/AMFEXA®/TENTIN®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Myocardial infarction, sudden death, serious ischaemic cardiac or cardiovascular disorders, cardiomyopathy • Stroke, TIA and other cerebrovascular accidents • Psychiatric disorders (incl. Psychotic symptoms, Suicidality, Aggression and hostility, Depression, Anorexia nervosa/anorexic disorders) • Tic/Tourette's/dystonia • Decreased rate of growth and development • Drug abuse, misuse and diversion • Dependence • Withdrawal syndrome
Important potential risks	• Off label use
Missing information	• Long-term safety (cardiovascular, neurological, cognitive and psychotic)

II.B Summary of important risks

Important identified risk: Myocardial infarction, sudden death, serious ischaemic cardiac or cardiovasvular disorders, cardiomyopathy	
Evidence for linking the risk to the medicine	Cases of myocardial infarction, stroke, and sudden death in children and adults taking ADHD stimulants have been reported. There is very little published literature on the occurrence of cardiomyopathy in persons with ADHD under amphetamine treatment and only a few case reports have been published. Most of reported cases of cardiomyopathy in connection with dexamfetamine use were cases in which dexamfetamine was overdosed, misused, or abused. In other cases, the cardiomyopathy can be ascribed to cardiac or cardiovascular preconditions rather than to dexamfetamine use. Cardiomyopathy can occur in patients receiving a therapeutic course of dexamfetamine/amphetamine; but it may be reversible with early diagnosis, identification of the cause and treatment.
Risk factors and risk groups	There are many risk factors associated with coronary heart disease, heart attack, angina (chest pain) and stroke. Behavioural risk factors include e.g. smoking, an unhealthy diet (e.g. high sodium or fat intake), high blood pressure, high blood cholesterol, overweight/obesity, and lack of physical exercise. Other risk factors include older age, diabetes and family history. Contributing risk factors for the development of cardiomyopathy may be long-term misuse of high doses/overdoses of amphetamines (drug dependence) as well as underlying cardiovascular diseases.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3 SmPC section 4.4 SmPC section 4.5 SmPC section 4.8 PL sections 2, 3, 4 Legal status: Prescription only medicine (special medical prescription, restricted medical prescription). Treatment must be under the supervision of a specialist in childhood and/or adolescent behaviour disorders.

	Additional risk minimisation measures: Prescriber Checklists
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Stroke, TIA and other cerebrovascular accidents	
Evidence for linking the risk to the medicine	Amphetamine use increases the odds of stroke by almost four times that of nonusers. Cases of stroke in patients using amphetamine have been reported in the scientific literature.
Risk factors and risk groups	Risk factors for cerebrovascular disorders such as stroke include hypertension (high blood pressure), atrial fibrillation (abnormal heart rhythm), smoking, poor diet, high blood cholesterol, lack of exercise, obesity, diabetes, excessive alcohol consumption, and stress.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3 SmPC section 4.4 SmPC section 4.5 SmPC section 4.8 PL sections 2, 3, 4 Legal status: Prescription only medicine (special medical prescription, restricted medical prescription). Treatment must be under the supervision of a specialist in childhood and/or adolescent behaviour disorders. Additional risk minimisation measures: Prescriber Checklists
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Psychiatric disorders (incl. Psychotic symptoms, Suicidality, Aggression and hostility, Depression, Anorexia nervosa/anorexic disorders)	
Evidence for linking the risk to the medicine	*Psychotic symptoms* There have been reports of children with ADHD who developed symptoms of psychosis or mania during treatment with amphetamine at usual doses. Psychotic and manic symptoms were reported as acute reactions in children with ADHD but without previous history of psychosis/mania as a mental illness. These acute reactions seemed to occur early in treatment as sporadic events at usual doses. *Suicidality and depression* Worsening of an underlying psychiatric condition like major depressive disorder (MDD) during dexamfetamine treatment was described in the literature. Depression is associated with an increased risk of suicidal thoughts. The depressive symptoms observed in children with ADHD being treated with stimulant drugs are similar in nature and severity to the depressive symptoms observed in children without ADHD. Reported symptoms range from a transient low mood with a duration of a few hours to a few days, to classic depressive symptoms, which sometimes progress to suicidal thoughts or suicidal behaviour. Children with ADHD who were treated with methylphenidate, amphetamines or placebo in clinical trials reported a range of adverse events that may be more appropriately categorised as situational reactions to life events, rather than a cluster of symptoms that would meet Diagnostic and Statistical Manual of Mental Disorders (DSM) V diagnostic criteria for major depression. *Aggression and hostility* Aggressive/hostile behaviour have been observed in and reported from children with ADHD being treated with stimulant drugs. It is a common co-morbid symptom in children with ADHD. Underlying aggression can be exacerbated by stimulant treatment. Aggressive behaviour has also been reported in children with ADHD with stimulant treatment, when previous aggressive behaviour did not exist. *Anorexia nervosa/anorexic disorders*

	Dexamfetamine can cause appetite suppression. This is a drug-induced pharmacological effect that resolves when the drug is discontinued. This was usually reported as "decreased appetite" or "anorexia" in clinical trials. While decreased appetite refers to a reduction in usual appetite, anorexia technically means absence of appetite, but is often used to convey a decrease in appetite. Anorexia (reduced appetite) needs to be distinguished from anorexia nervosa, a serious eating disorder that can be associated with co-morbidities and even mortality. Drug-induced anorexia is not a chronic eating disorder, but a reversible side effect associated with stimulant medications. Nonetheless, patients with a diagnosis or history of anorexia nervosa may be at increased risk of worsening or reappereance of this condition.
Risk factors and risk groups	Patients at risk comprise those with a diagnosis or history of psychiatric disorders such as severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, hyperexcitability, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder. Risk factors for psychotic reactions in the form of e.g. paranoid symptoms can also be psychosocial stress or overdose of dexamfetamine. Further risk factors for suicidal thoughts may include being female, younger, less educated, unmarried, and having a mental disorder. Post-traumatic stress disorder seems to be an important risk factor. Sleep disturbances, e.g. insomnia, nightmares, etc., are associated with suicidal ideation, too. Additionally, risk factors for depression may also include – among others - female sex, a positive family history, suicide in family history, stress, serious disease, low self-esteem, alcohol abuse, drug abuse, and a low socioeconomic group.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3 SmPC section 4.4 SmPC section 4.8 PL sections 2, 3, 4 Legal status: Prescription only medicine (special medical prescription, restricted medical prescription). Treatment must be under the supervision of a

	specialist in childhood and/or adolescent behaviour disorders. Additional risk minimisation measures: Prescriber Checklists
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Tic/Tourette's/dystonia	
Evidence for linking the risk to the medicine	Studies have shown that high doses of dexamfetamine can worsen tics. Although, overall, stimulants have not been shown to worsen tics in most participants with tic disorders, they may still worsen tics in individual cases.
Risk factors and risk groups	The development or worsening of pre-existing tics are considered to very rarely occur with amphetamine treatment. Tics may be triggered or worsened by stress, anxiety, excitement, exhaustion, or environmental factors like gesture or sound. Other risk factors include maternal smoking or complications during pregnancy and lower birth weight.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3 SmPC section 4.4 SmPC section 4.8 PL sections 2, 3, 4 Legal status: Prescription only medicine (special medical prescription, restricted medical prescription). Treatment must be under the supervision of a specialist in childhood and/or adolescent behaviour disorders. Additional risk minimisation measures: Prescriber Checklists
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Decreased rate of growth and development	
Evidence for linking the risk to the medicine	A common side effect of amphetamines is loss of appetite, resulting in slower weight gain. A clinical study showed that treatment with amphetamine (lisdexamfetamine) is associated with reductions in expected height, weight, and body mass index (BMI) in children with ADHD.
Risk factors and risk groups	Risk groups are children and adolescents until growth of height is accomplished; growth delays are greatest for the heaviest and tallest children, for those who had not previously received stimulant therapy, and for those with a greater cumulative exposure to amphetamine.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 SmPC section 4.8 PL sections 3, 4 Legal status: Prescription only medicine (special medical prescription, restricted medical prescription). Treatment must be under the supervision of a specialist in childhood and/or adolescent behaviour disorders. Additional risk minimisation measures: Prescriber Checklists
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Abuse, misuse and diversion	
Evidence for linking the risk to the medicine	As per scientific knowledge, dexamfetamine has no effect on whether children abuse alcohol, marijuana, nicotine or cocaine later in life. In scientific literature the risk for abuse and dependency of ADHD drugs has been reported. Appropriate use, including prescription use only, and only if really needed for ADHD, is strongly endorsed.
Risk factors and risk groups	Patients with a history of drug dependence or alcohol abuse are potentially at risk as these patients may be more likely to abuse stimulant medication.

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 SmPC section 4.4 PL section 3 Legal status: Prescription only medicine (special medical prescription, restricted medical prescription). Treatment must be under the supervision of a specialist in childhood and/or adolescent behaviour disorders. Additional risk minimisation measures: Prescriber Checklists Healthcare Professional Guide Parent/Carer Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Dependence	
Evidence for linking the risk to the medicine	The risk of dependence to ADHD drugs has been reported in the scientific literature. In addition, individual case safety reports have been issued. The strength of evidence is undisputed.
Risk factors and risk groups	Risk factors include dependence to other drugs or alcohol as well as long-term use and use in high (non-therapeutic) doses. Risk groups are patients or subjects committing misuse, abuse or overdose or other wrong use of the drug and long-term users.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 SmPC section 4.3 SmPC section 4.4 SmPC section 4.8 PL sections 2, 3, 4 Legal status: Prescription only medicine (special medical prescription, restricted medical prescription).

	Treatment must be under the supervision of a specialist in childhood and/or adolescent behaviour disorders. Additional risk minimisation measures: Prescriber Checklists Healthcare Professional Guide Parent/Carer Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Withdrawal syndrome	
Evidence for linking the risk to the medicine	When chronic heavy users abruptly discontinued amphetamine use, many of them reported a time-limited withdrawal syndrome that occurred within 24 hours since intake of their last dose. Withdrawal symptoms are sufficiently severe to cause relapse to drug use in the absence of contained environments.
Risk factors and risk groups	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. If in consequence, amphetamine dependence due to misuse of amphetamine occurs, then withdrawal is common when the drug is not available. The severity of withdrawal symptoms is greater in amphetamine-dependent individuals who are older and who have more extensive amphetamine use disorders.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 SmPC section 4.4 SmPC section 4.8

	PL section 4 Legal status: Prescription only medicine (special medical prescription, restricted medical prescription). Treatment must be under the supervision of a specialist in childhood and/or adolescent behaviour disorders. Additional risk minimisation measures: Prescriber Checklists
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Off-label use	
Evidence for linking the risk to the medicine	Studies have shown that misuse of prescription ADHD medications occurs in 5% to 9% of grade school- and high school-age children and 5% to 35% in college-age individuals. 16% to 29% of students with stimulant prescriptions have been asked to give, sell, or trade their medications. The most commonly reported reasons for use of non-prescribed stimulants include studying, staying awake, improved alertness, "getting high" / "partying", and experimenting.
Risk factors and risk groups	Patients with a history of drug dependence or alcohol abuse are potentially at risk as these patients may be more likely to misuse stimulant medications. Studies have shown that misuse of prescription ADHD medications occurs in 5% to 9% of grade school- and high school-age children and 5% to 35% in college-age individuals. 16% to 29% of students with stimulant prescriptions have been asked to give, sell, or trade their medications. The most commonly reported reasons for use of non-prescribed stimulants include studying, staying awake, improved alertness, "getting high" / "partying", and experimenting.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 PL section 1, 3 Legal status: Prescription only medicine (special medical prescription, restricted medical prescription). Treatment must be under the supervision of a specialist in childhood and/or adolescent behaviour disorders.

	Additional risk minimisation measures: Prescriber Checklists Healthcare Professional Guide Patient/Carer Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None. See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term safety (cardiovascular, neurological, cognitive and psychotic)	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 SmPC section 4.4 PL section 3 Legal status: Prescription only medicine (special medical prescription, restricted medical prescription). Treatment must be under the supervision of a specialist in childhood and/or adolescent behaviour disorders. Additional risk minimisation measures: Prescriber Checklists
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of ATTENTIN®/AMFEXA®/TENTIN®.

II.C.2 Other studies in post-authorisation development plan

Not applicable.