VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Attention-deficit hyperactivity disorder (ADHD) is a mental disorder that involves difficulty paying attention, hyperactivity and impulsive behavior. ADHD starts during childhood and can continue into adulthood. It is estimated that between 2 and 18% of school-age children, and about 3% of adults aged 18 to 44 years have ADHD. People with untreated ADHD have twice the risk for cigarette smoking and substance abuse. Young people with ADHD are also at a higher risk for suicidal behavior. ADHD is linked with other mental disorders such as anxiety, depression and learning disorder.

VI.2.2 Summary of Treatment Benefits

Lisdexamfetamine has been shown to be an effective and well tolerated treatment for ADHD. In 10 studies in ADHD, lisdexamfetamine was more effective when compared to placebo (a pill that contains no medicine). In studies enrolling children, adolescents, and adults with ADHD, the use of lisdexamfetamine led to marked improvement in ADHD symptoms, functional outcomes, and quality of life as compared to placebo, as demonstrated using a variety of study designs, a variety of validated assessments, and with data provided by investigators, parents, trained raters, and self-reports. Lisdexamfetamine was effective over the treatment day for both children (13-hour duration) and adults (14-hour duration). In studies where assessments were measured weekly, lisdexamfetamine was effective at the first treatment visit and was maintained until the end of the study.

VI.2.3 Unknowns Relating to Treatment Benefits

Most of the research on lisdexamfetamine has been conducted in the USA. Although, clinical studies in Europe have demonstrated that lisdexamfetamine is effective in the treatment of ADHD. Doctors are missing information on the long term safety of lisdexamfetamine in children and adolescents.

VI.2.4 Summary of Safety Concerns

Table 67: Important Identified Risks

Risk	What is Known	Preventability
Abnormally fast/uneven heart rate (tachycardia)	Less than 1 in 10 adults and less than 1 in 100 children using lisdexamfetamine will get symptoms.	Yes Patients should be monitored for large changes in heart rate. Patients with heart disease and conditions like high blood pressure should not take lisdexamfetamine.
Long-term disease of the heart muscle (cardiomyopathy)	This condition is very infrequent in patients who take lisdexamfetamine as prescribed. Patients who abuse amfetamines may develop this condition.	Yes Patients should have pre-treatment screening and ongoing monitoring of cardiovascular status.
High blood pressure (hypertension)	This is known to affect less than 1 in 100 children and less than 1 in 10 adolescents and adults using lisdexamfetamine.	Yes Patients with moderate or severe high blood pressure should not take lisdexamfetamine
Loss of appetite (decreased appetite)	This is known to affect more than 1 in 10 people using lisdexamfetmine.	Yes Patients should have weight and appetite checked before and during treatment.

Table 67: Important Identified Risks

Risk	What is Known	Preventability
Slow growth or development (growth retardation and developmental delay in children and adolescents)	This is a known risk for stimulant medications.	Yes Patients should have growth checked during treatment. Patients who are not growing or gaining weight may need to stop treatment.
Seeing, hearing or feeling things that are not real (hallucinations)	This is known to affect less than 1 in 100 children and adolescents using lisdexamfetmine.	Yes Patients should have ongoing monitoring for psychiatric disorders. Agitated patients should not use lisdexamfetamine.
Feeling usually excited, overactive or uninhibited (mania)	This is known to affect less than 1 in 100 children and adults using lisdexamfetamine.	
Feeling agitated, aggressive and irritable (hostility/aggression)	This known to affect less than 1 in 100 of children and adolescents, and less than 1 in 10 adults using lisdexamfetamine.	
Feeling sad (Depression)	This is known to affect less than 1 in 100 of children, adolescents and adults using lisdexamfetamine.	
Uncontrolled twitching or jerking of the body (tics)	This is known to affect less than 1 in 10 children and less than 1 in 100 adults using lisedexamfetamine.	Yes. Clinical evaluation should be done to check for tics and tourettes syndrome in patients and their families before treatment.
Intentional drug abuse (Intentional drug misuse, drug abuse and diversion)	This is a known risk for stimulant medications for ADHD.	Yes Patients should be monitored for signs of misuse, abuse or diversion of lisdexafetamine. Prescribers are urged to consider the potential of misuse, abuse or diversion before prescribing.
Serious skin reactions	Serious skin reactions are very unusual with lisdexamfetamine.	If drug related the medicine should be stopped immediately.
A disorder causing blood vessels to spasm when exposed to cold (Raynaud's phenomenon)	Raynaud's phenomenon is a known risk for stimulant medications.	Yes The lowest clinically effective dose should be used.

Table 68: Important Potential Risks

Risk	What is Known
Problems resulting from too little blood supply to the heart (ischaemic cardiac	Stimulants medicines like lisdexamfetamine can cause high blood pressure, irregular heart beat, which might result in too little blood supply to the heart, and heart attack. Adults are more likely than children to have serious heart problems.

Table 68: Important Potential Risks

Risk	What is Known
events)	
Sudden death	Some children and adults with existing heart problems have died suddenly after taking stimulant medicines.
Symptoms after stopping the medicine (Withdrawal syndrome)	No testing has been performed to find out if patients can become tolerant or dependent to lisdexamfetamine. Medicines of the same type have these effects so it is likely that lisdexamfetamine could be the same.
Suicide(Suicidality)	Available evidence including lisdexamfetmaine safety data and literature indicates that lisdexamfetamine does not increase the rate of suicide and related events. Patients with ADHD are 2-3 times more likely to try or think about suicide so the risk is mainly linked to the disease itself.
Migraine	Lisdexamfetamine causes headache though there is not enough evidence to establish an association between migraine and lisdexamfetamine. Food is an important trigger for migraine. Lisdexamfetamine affects appetite so some patients who skip meals because they have reduced appetite may get more frequent headaches.
Fainting or passing out (Syncope)	There is no known reason why lisdexamfetamine should cause fainting. However stimulants like lisdexamfetamine are linked with high blood pressure, irregular heart beat and other heart problems. Heart disease itself can cause fainting but most patients who faint do not have any serious disorder.
Cancer (Carcinogenicity)	There is no evidence that lisdexamfetamine causes cancer. However, there is no long-term information in humans.
Heart and lung damage to newborn children (neonatal cardio-respiratory toxicity)	There is no known reason why lisdexamfetamine should cause heart or lung problems in babies; medicines like lisdexamfetamine go into breast milk. Breastfeeding mothers should not use lisdexamfetamine.
Effect on growth in newborns from breast milk (neonatal effects on growth (via lactation)	Stimulants cause weight loss and slowing of growth rate in children. There is no published evidence supporting a mechanism. However, medicines like lisdexamfetamine go into breast milk. The appetite of the baby might be affected and could lead to weight loss.
Use of the medicine other than approved by Regulatory authorities (Off-label use)	Lisdexamfetmine is not for use in children below 6 years of age. It should only be used to treat ADHD. Sometimes doctors do prescribe it for these very young children, or for other conditions, but these are not approved uses of lisdexamfetamine.
Disorders of the blood vessels in the brain (cerebrovascular disorders (ischaemic and haemorrhagic strokes)	Patients who get high blood pressure from taking stimulants like lisdexamfetamine may get bleeding problem or swelling of the blood vessels in the brain.

Table 69: Missing Information

Risk	What is Known
Long-term safety in adults	There is limited information about the long term effects of lisdexamfetamine to

	the heart and brain and blood vessels in adults.
Safety in pregnant women	There is limited information about use in pregnancy. Therefore, lisdexamfetamine should only be used in pregnancy if the likely benefit justifies the possible risk to the unborn child.
Safety in the elderly	There is limited information available about use in the elderly.

VI.2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the Patient Information Leaflet. The measures in these documents are known as routine risk minimisation measures.

The SmPC and the Patient Information Leaflet for ELVANSE/TYVENSE/ELVANSE ADULT/ ELVANSE VUXEN/ADUVANZ can be found on national websites.

Additionally Shire (the company that makes lisdexamfetamine) has developed a web-based educational tool for doctors. This also tells them how to use lisdexamfetamine. Before doctors can use it, the Department of Health in each country has to approve it.

VI.2.5.1 Safety Concern in Lay Terms (Medical Term)

See Section VI.2.4 for details of the safety concerns.

Risk Minimisation Measure(s): Web-based Educational Tool for Prescribers
Objective and Rationale: The website and downloadable tools aim to help doctors and healthcare staff make sure they only give lisdexamfetamine to the correct patients with attention-deficit/hyperactivity disorder. There are checklists and a chart to help them. The website also contains a downloadable educational leaflet for patients and their parents/guardians.
Summary description of main additional risk minimisation measures To assist physicians with use of lisdexamfetamine according to the Summary of Product Characteristics. Shire developed a web-based educational tool for prescribers that contain checklists for actions before prescribing lisdexamfetamine and monitoring for patients continuing on the treatment. The content on the website is based on the lisdexamfetamine Summary of Product Characteristics. The website is available in the appropriate national languages.

VI.2.6 Planned Post Authorisation Development Plan

Table 70: List of Studies in Post-authorisation Development Plan

Study/Activity, Type, Title and Category (1-3)	Objectives	Safety Concerns/Efficacy Issue Addressed	Status	Planned Date for Submission of (Interim and) Final Results
Drug utilisation study for ELVANSE/TYVENSE in Europe	The overall objective is to provide utilisation data, on an annual basis for up to 5 years following launch, to allow an evaluation of off-label use. Study objectives in detail: -To characterise patients who are prescribed ELVANSE -To describe prescribing patterns of ELVANSE among physicians -To describe usage patterns of ELVANSE among patients -To monitor presence of cardiovascular and cerebrovascular comorbidities in patients on Elvanse®/Tyvense®1 in order to measure the effectiveness of the risk minimization measures	Off-label use	Ongoing	Annually for 5 years. First & second reports have been submitted with the PSUR in April 2014& 2015. .
Pharmacoepidemiology study Non-interventional retrospective post authorisation study Title- SPD489-825: Cohort Study of the Incidence of Major Cardiovascular Events in New Adult Users of Lisdexamfetamine and Remote Adult Users of Other ADHD Treatments Category 2	The primary objective of this study is to estimate, in real-world settings, the incidence rate and the adjusted incidence rate ratios of the composite major adverse cardiovascular events (MACE) endpoint in a cohort of adult patients who are current new users of LDX (the LDX cohort) compared with a cohort of remote users of other ADHD treatments in three European data sources	Long-term safety (cardiovascular and cerebrovascular effects) in adults	Planned	Final report in 2020 (planned)

VI.2.6.1 Studies which are a Condition of the Marketing Authorisation.

None of the above studies are conditions of the marketing authorisation

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Table 71: Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
1.2	At time of authorisation 22 Oct 2012	**Identified risks** • Tachycardia • Cardiomyopathy • Increased blood pressure • Anorexia • Growth retardation and developmental delay • Hallucinations (auditory, skin sensation, visual disturbance) • Psychosis/Mania • Hostility/Aggression • Depression • Tics • Intentional drug misuse and abuse • Serious skin reactions • Diversion **Potential risks** • Ischaemic cardiac events • Sudden death • Withdrawal syndrome • Suicidality • Migraine • Syncope • Carcinogenicity • Neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia, respiratory distress/apnoea) • Neonatoal effects on growth (via lactation) • Off-label use • Cerebrovascular disorders (ischaemic and haemorrhagic stroke) • Raynaud's phenomenon **Missing information** • Long-term safety (cardiovascular, cerebrovascular, and psychiatric effects) • Safety in pregnant women • Safety in the elderly	Approved by Health Authority 16 Dec 2012

Table 71: Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
2.0 (Not approved)	19 Dec 2013	Intentional drug misuse, abuse and diversion merged as 1 risk. Serious skin reactions risk removed as no further characterisation required Otherwise same as Version 1.2	At the time of filing for adult indication
2.1 (Not approved)	August 2014	**Identified risks** • Serious skin reactions reinstated as an identified risk • Raynaud's phenomenon changed from potential to identified risk • The risk term 'Anorexia' changed to 'Decreased appetite'. • The risk term 'Growth retardation and developmental delay' was changed to 'Growth retardation and developmental delay in children and adolescents' **Missing information** • The risk tem 'Long-term safety (cardiovascular, cerebrovascular, and psychiatric effects)' changed to 'Long-term safety (cardiovascular, cerebrovascular, and psychiatric effects) in children and adolescents' Otherwise same as Version 1.2	Addressed at the time of the response to D105 comments for the Adult indication As of a result of a change in adverse event coding in MedDRA v12.0, the PT 'anorexia' was demoted to a lower-level term (LLT) under the PT 'decreased appetite' Therefore the risk term has been changed from "Anorexia" to "Decreased appetite" in the RMP
2.2	November 2014		Addressed at the time of the response to D120 comments for the Adult indication
2.3	January 2015	Long-term safety (cardiovascular and cerebrovascular effects) in adults added as missing information. Otherwise same as previous version	Addressed at the time of the response to D180 comments for the Adult indication
2.4	January 2015	Same as version 2.3	Updated to include new strengths (20mg, 40mg, and 60mg). Procedure is ongoing
3.0	May 2015	'Long-term safety (cardiovascular, cerebrovascular, and psychiatric effects) in children and adolescents' removed as missing information, based on the findings from study SPD489-404, which showed that there was no new or unexpected safety signals with the administration of LDX for 2 years. Otherwise same as version 2.3	At the time of completion of milestone (SPD489-404)
3.1	November 2015	Interaction with serotonergic drugs was included in the 'important identified and	Updated following CCDS and local labelling

Table 71: Major Changes to the Risk Management Plan Over Time			
Version	**Date**	**Safety Concerns**	**Comment**
		potential interactions' section. Otherwise, same as version 3.0	changes