# Part VI: Summary of the risk management plan

## Summary of risk management plan for ELVANSE®/ TYVENSE®/ ELVANSE ADULTOS®/ ELVANSE VUXEN®/ ADUVANZ® (Lisdexamfetamine dimesylate)

This is a summary of the risk management plan (RMP) for ELVANSE®/ TYVENSE®/ ELVANSE ADULTOS®/ ELVANSE VUXEN®/ ADUVANZ®. The RMP details important risks of ELVANSE®/ TYVENSE®/ ELVANSE ADULTOS®/ ELVANSE VUXEN®/ ADUVANZ®, how these risks can be minimised, and how more information will be obtained about ELVANSE®/ TYVENSE®/ ELVANSE ADULTOS®/ ELVANSE VUXEN®/ ADUVANZ®'s risks and uncertainties (missing information).

ELVANSE®/ TYVENSE®/ ELVANSE ADULTOS®/ ELVANSE VUXEN®/ ADUVANZ® SmPC and its package leaflet give essential information to healthcare professionals and patients on how ELVANSE®/ TYVENSE®/ ELVANSE ADULTOS®/ ELVANSE VUXEN®/ ADUVANZ®should be used.

Important new concerns or changes to the current ones will be included in updates of ELVANSE®/ TYVENSE®/ ELVANSE ADULTOS®/ ELVANSE VUXEN®/ ADUVANZ®'s RMP.

### I. The medicine and what it is used for

ELVANSE®/ TYVENSE®/ ELVANSE ADULTOS®/ ELVANSE VUXEN®/ ADUVANZ® is authorised for attention-deficit hyperactivity disorder - (see SmPC for the full indication). It contains Lisdexamfetamine dimesylate as the active substance and it is given orally.

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

Important risks of ELVANSE®/ TYVENSE®/ ELVANSE ADULTOS®/ ELVANSE VUXEN®/ ADUVANZ®'s, together with measures to minimise such risks and the proposed studies for learning more about ELVANSE®/ TYVENSE®/ ELVANSE ADULTOS®/ ELVANSE VUXEN®/ ADUVANZ®'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 so 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 ELVANSE®/ TYVENSE®/ ELVANSE ADULTOS®/ ELVANSE VUXEN®/ ADUVANZ®, 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 continually and regularly analyzed, including Periodic safety update report (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 ELVANSE®/ TYVENSE®/ ELVANSE ADULTOS®/ ELVANSE VUXEN®/ ADUVANZ® is not yet available, it is listed under 'missing information' below.

### II.A List of important risks and missing information

Important risks of ELVANSE®/ TYVENSE®/ ELVANSE ADULTOS®/ ELVANSE VUXEN®/ ADUVANZ® 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 ELVANSE®/ TYVENSE®/ ELVANSE ADULTOS®/ ELVANSE VUXEN®/ ADUVANZ®. 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** | |
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| Important identified risks | 1. Intentional drug misuse, abuse and diversion<br>2. Growth retardation and developmental delay in children and adolescents<br>3. Psychosis/Mania<br>4. Hostility/Aggression<br>5. Depression |
| Important potential risks | 1. Serious cardiovascular events (including arrhythmias, ischaemic cardiac events, cardiomyopathy, sudden death)<br>2. Cerebrovascular disorders (ischaemic and haemorrhagic stroke)<br>3. Syncope<br>4. Suicidality<br>5. Off-label use<br>6. Neonatal effects on growth (via lactation) |
| Missing information | 1. Safety in pregnant women<br>2. Safety in the elderly<br>3. Long-term safety (cardiovascular and cerebrovascular effects) in adults |

### II.B Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product.

| **Important identified risk:** Intentional drug misuse, abuse and diversion | |
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| **Evidence for linking the risk to the medicine** | Reports of misuse, abuse and diversion of LDX have been received via post-marketing surveillance and are databased in the Shire Global Safety System |
| **Risk factors and risk groups** | Identified risk factors for substance abuse in adolescents and young adults include living in poverty, ineffective parenting, having a caregiver who abuses drugs, poor classroom behaviour or social skills, academic failure, and |

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| | association with drug- abusing peers [168].<br>Factors identified in adults for any prescription drug nonmedical use include: the age group 18-25 years, male sex, white race, and not beingmarried [169]. |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br>Misuse and abuse monitoring stipulation in Section 4.2 of the SmPCDrug abuse and misuse warning in Section 4.4 of the SmPC Diversion monitoring stipulation in Section 4.2 of the SmPC Diversion warning in Section 4.4 of the SmPC.<br>**Additional risk minimisation measures:**<br>Educational tools. |
| **Additional pharmacovigilance activities** | **Additional pharmacovigilance activities:**<br>None |
| **Important identified risk:** Growth retardation and developmental delay in children and adolescents | |
| **Evidence for linking the risk to the medicine** | Growth retardation and developmental delay related to therapy with LDXhave been documented in Shire Global Safety System, and scientific literature. |
| **Risk factors and risk groups** | Risk factors for growth retardation among children and adolescents include chronic undernutrition, infectious disease, restricted intrauterinegrowth [170], and preterm birth [171].<br>Risk factors for developmental delays include living in a low-income household[44], being of low birth weight [172], having foetal alcohol syndrome, genetic, and behaviouralconditions, and having infections (CDC 2005). |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br>Pre-treatment growth monitoring stipulation in Section 4.2 of the SmPCGrowth warning in Section 4.4 of the SmPC<br>This risk is addressed in Section 4.8 (Undesirable effect) of the SmPC.<br>**Additional risk minimisation measures:**<br>Educational tools. |
| **Additional pharmacovigilance activities** | **Additional pharmacovigilance activities:**<br>None |
| **Important identified risk:** Psychosis/Mania | |
| **Evidence for linking the risk to the medicine** | Clinical studies; post-marketing data. |

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| **Risk factors and risk groups** | In the Massachusetts General Hospital study, children with ADHD and comorbid mania at either the baseline or the follow-up assessment had otherclinical predictors expected in the disorder. These correlates included other psychopathology, psychiatric hospitalisation, severely impaired psychosocial functioning, and a family history of mood disorders [173].<br><br>A recent cohort study using health claim data in US [174] revealed that among adolescents and young adults with ADHD who were receiving prescription stimulants, new-onset psychosis occurred in approximately 1 in 660 patients. Amphetamine use was associated with a greater risk of psychosis than methylphenidate (hazard ratio 1.65; 95% CI,1.31 - 2.09). |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br><br>Pre-treatment screening for psychiatric disorders stipulation in Section 4.2 ofthe SmPC<br><br>Psychiatric adverse events warning Section 4.4 of the SmPC Also addressed in Section 4.8 (Undesirable effect) of the SmPC.<br><br>**Additional risk minimisation measures:**<br><br>Educational tools. |
| **Additional pharmacovigilance activities** | **Additional pharmacovigilance activities:**<br><br>None |
| **Important identified risk:** Hostility/Aggression | |
| **Evidence for linking the risk to the medicine** | Clinical studies, post-marketing and scientific literature. |
| **Risk factors and risk groups** | In an Australian cross-sectional population study, males were 1.87 timesmore likely to be diagnosed as aggressive [175]. In a cluster analysis of 406 children, 10% of boys demonstrated physical violence compared to 5.3% of girls [176].<br><br>In an Australian population study of toddlers, children, and teens, impulsive- hyperactive ADHD children were 12.63 times more likely to be scored as aggressive; inattentive and combination ADHD children werelikely to be scored as delinquent or with conduct disorder (2.71 and 4.00 and 3.21 and 2.91, respectively [175].<br><br>Aggression and hostility may be higher among those with comorbidmental illness in the elderly population [177]. |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br><br>Pre-treatment screening for psychiatric disorders stipulation in Section 4.2 ofthe SmPC |

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| | Contraindication in Section 4.3 of the SmPC<br><br>Psychiatric adverse events warning in Section 4.4 of the SmPCAlso addressed in Section 4.8 (Undesirable effect) of the SmPC<br><br>**Additional risk minimisation measures:**<br><br>Educational tools. |
| **Additional pharmacovigilance activities** | **Additional pharmacovigilance activities:**<br><br>None |
| **Important identified risk:** Depression | |
| **Evidence for linking the risk to the medicine** | Clinical studies; post-marketing, scientific literature. |
| **Risk factors and risk groups** | Identified risk factors for depression in adolescents (most often defined as14-19 years of age) include female sex, family history of depressive episodes, conflict with parents, and elevated symptoms of borderline personality disorder [178]. In adults, risk factors for depression were identified in a large population survey from the US of those aged 18-44 years [179]. Factors related to increased risk were: female sex (RR=1.5), marital separation or divorce (RR=1.9), and being employed (RR=0.6). |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br><br>Pre-treatment screening for psychiatric disorders stipulation in Section 4.2 of the current SmPC<br><br>Psychiatric adverse events warning Section 4.4 of the SmPC Also addressed in Section 4.8 (Undesirable effect) of the SmPC.<br><br>**Additional risk minimisation measures:**<br><br>Educational tools. |
| **Additional pharmacovigilance activities** | **Additional pharmacovigilance activities:**<br><br>None |
| **Important Potential risk:** Serious cardiovascular events (including arrhythmias, ischaemic cardiac events, cardiomyopathy, sudden death) | |
| **Evidence for linking the risk to the medicine** | Clinical studies; post-marketing, scientific literature. |
| **Risk factors and risk groups** | There are a wide variety of factors that influence the development of serious cardiovascular disorders in the general population including personal characteristics such as age (more frequent in elderly), sex (more common in male), race, weight (obesity), genetic factors (or family history), environmental factors and life styles including occupation, smoking, alcohol use and substance abuse. |

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| | Pre-existing congenital or acquired cardiovascular conditions are clear predisposing factors for serious cardiovascular disorders and serious outcomes. |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br>This risk is addressed in Section 4.2, Section 4.3, Section 4.4, Section 4.8,Section 4.9 of the SmPC.<br>**Additional risk minimisation measures:**<br>Educational tools. |
| **Additional pharmacovigilance activities** | **Additional pharmacovigilance activities:**<br>None |
| **Important potential risk**: Cerebrovascular disorders (ischaemic and haemorrhagic stroke) | |
| **Evidence for linking the risk to the medicine** | Among young adults 18-44 years old who were hospitalised in Texas between 2000 and 2003, amfetamine abuse was associated with a 5-fold increase in the risk for haemorrhagic stroke. Cocaine use increases the risk for haemorrhagic stroke to a lesser extent than amfetamine use, but also increasesthe risk for ischaemic stroke [180]. |
| **Risk factors and risk groups** | Age, hypertension, cigarette smoking, atrial fibrillation, asymptomatic carotid stenosis, hyperlipidemia, positive family history, previous stroke or transient ischaemic attack, obesity, and diabetes are known risk factors for stroke |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br>This risk is addressed in Sections 4.2, 4.3, and 4.4 of the SmPC.<br>**Additional risk minimisation measures:**<br>Educational tools. |
| **Additional pharmacovigilance activities** | **Additional pharmacovigilance activities:**<br>None |
| **Important potential risk:** Syncope | |
| **Evidence for linking the risk to the medicine** | Stimulants, including LDX, may cause the unmasking or worsening of pre-existing hypertension, arrhythmia, and ischaemic events due to the adrenergic effect on the heart and blood pressure. Syncopal events can be indicative of cardiac disease. To date, evidence for LDX and syncopal events do not support syncope events as an identified risk. |
| **Risk factors and risk groups** | Patients with cardiac disease<br>• Obstruction to left ventricular outflow or inflow e.g., aortic valvestenosis<br>• Obstruction to right ventricular outflow or inflow: |

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| | e.g., pulmonic stenosis<br>• Other heart disease: e.g., pump failure, myocardial infarction<br>• Arrhythmias (4–38% of patients)<br>Patients with neurological disease<br>• Migraine<br>Transient ischaemic attacks |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br>Exertional chest pain, unexplained syncope, or other symptoms suggestive ofcardiac disease warning in Section 4.4 of the SmPC .<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |
| **Additional pharmacovigilance activities** | **Additional pharmacovigilance activities**:<br>None |
| **Important Potential Risk:** Suicidality | |
| **Evidence for linking the risk to the medicine** | Scientific literature, clinical studies and post-marketing reports |
| **Risk factors and risk groups** | Among persons with ADHD, conduct disorder is another common comorbidity and has been shown to be associated with elevated risk of suicidal behaviour. A 15-year follow-up study of children with hyperactivity found those with persistent antisocial behaviour to have greater risk of a suicide attempt (31.5% versus 0%, p=0.02) [57]. A case-control study of children with disruptive disorders (ADHD and/or conduct disorder) found suicide victims to have a higher prevalence of conduct disorder than controls (odds ratio, 2.9; 95% CI, and 1.0–8.8). The same study also found family history of mood disorders (odds ratio, 2.3; 95% CI, 1.0–5.5) and substance abuse (odds ratio, 7.4; 95% CI, 1.7–31.4) to be associated with suicide [181]. Suicidal ideation is a risk factor for suicide attempt and completed suicide. Repetition of attempts further increases the risk of suicide. A history of previous attempted suicide isthe most important independent predictor of repetition (odds ratio 3.2, 95% CI2.4–4.4; [182]. Mental disorders are the most common risk factors for suicide in all age groups. A review of studies of completed suicides estimated that 30.2% of cases were associated with mood disorders, 17.6% with substance-related disorders, 14.1% with schizophrenia, 13.0% with personality disorders, and 16.7% with other disorders; only 2.0% of cases had no associated mental disorders [183]. An investigation of suicidal ideation and suicide attempts among youth ages 9–17 obtained a hazard ratio for depression of 8.5 (95% CI, 4.5–15.9) [184]. This study |

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| | found that alcohol abuse or dependence was highly predictive of suicide attempts (odds ratio, 25.2; 95% CI, 4.6–129.2). Daily use of cigarettes also predicted suicide attempts (odds ratio, 5.0; 95% CI, 1.2–19.4) [184]. In a Swedish register based longitudinal study of 37,936 patients with ADHD no evidencewas found for a positive association between the use of drug treatments forADHD and the risk of concomitant suicidal behaviour among patients with ADHD. The authors concluded that, if anything, the results pointed to a potential protective effect of drugs for ADHD on suicidal behaviour, particularly for stimulant drugs [41]. |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br>This risk is addressed in Sections 4.2 and 4.4 of the SmPC.<br>**Additional risk minimisation measures:**<br>Educational tools. |
| **Additional pharmacovigilance activities** | **Additional pharmacovigilance activities**:<br>None |
| **Important Potential Risk:** Off-label use | |
| **Evidence for linking the risk to the medicine** | Spontaneous reports from post-marketing surveillance. |
| **Risk factors and risk groups** | Not applicable |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br>Off-label age groups addressed in Section 4.2 (*Special populations*) ofthe SmPC.<br>**Additional risk minimisation measures:**<br>Educational tools. |
| **Additional pharmacovigilance activities** | **Additional pharmacovigilance activities**:<br>None |
| **Important Potential Risk:** Neonatal effects on growth (via lactation) | |
| **Evidence for linking the risk to the medicine** | Spontaneous reports from post-marketing surveillance. |
| **Risk factors and risk groups** | Not applicable |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br>Breastfeeding is addressed in Section 4.6 of the SmPC.<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |

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| **Additional pharmacovigilance activities** | **Additional pharmacovigilance activities**:<br>None |
| **Missing Information:** Safety in pregnant women | |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br>Pregnancy is addressed in Section 4.6 of the SmPC.<br>**Additional risk minimisation measures:**<br>Educational tools. |
| **Additional pharmacovigilance activities** | **Additional pharmacovigilance activities**:<br>None |
| **Missing Information:** Safety in the elderly | |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br>Elderly addressed in Section 4.2 (*Special populations*) of the SmPC<br>**Additional risk minimisation measures:**<br>No risk minimisation activities |
| **Additional pharmacovigilance activities** | **Additional pharmacovigilance activities**:<br>None |
| **Missing Information:** Long-term safety (cardiovascular andcerebrovascular effects) in adults | |
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br>Long-term safety is addressed in Section 4.2 (*Special populations*) of theSmPC<br>**Additional risk minimisation measures:**<br>No risk minimisation activities |
| **Additional pharmacovigilance activities** | **Additional pharmacovigilanceactivities:**<br>None |

**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 LDX.

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

None.