Summary of Risk Management Plan for Xeristar (duloxetine)

This is a summary of the RMP for Xeristar. The RMP details important risks of Xeristar, how these risks can be minimised, and how more information will be obtained about Xeristar's risks and uncertainties (missing information).

Xeristar's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Xeristar should be used.

This summary of the RMP for Xeristar should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the EPAR.

Important new concerns or changes to the current concerns will be included in updates of Xeristar's RMP.

I - The Medicine and What It is Used for

Xeristar is authorised for MDD, DPNP, and GAD (see the SmPC for the full indication). Xeristar contains duloxetine as the active substance and is given by oral administration.

Further information about the evaluation of Xeristar's benefits can be found in Xeristar's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000573/human_med_001159.jsp&mid=WC0b01ac058001d124.

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Xeristar, together with measures to minimise such risks and the proposed studies for learning more about Xeristar'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.

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

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 PV activities.

If important information that may affect the safe use of Xeristar is not yet available, it is listed under 'missing information' below.

II.A Xeristar List of Important Risks and Missing Information

Important risks of Xeristar 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 Xeristar. 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 (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Suicidality
Missing information	Prospective data about potential risks of exposure to duloxetine during pregnancy

II.B Xeristar Summary of Important Risks

Important identified risk: Suicidality	
Evidence for linking the risk to the medicine	Suicidality has been considered a class effect across different antidepressant medicines for many years. With the exception of young adults and paediatric patients, the evidence linking duloxetine with suicidality is weak, with multiple evidence sources indicating that patients taking duloxetine are not at higher risk for suicidality when compared with placebo-treated patients. These data sources include meta-analyses conducted by Lilly and the US Food and Drug Administration (FDA) regulatory agency, as well as data from observational studies. The incidence estimates of suicidality in duloxetine-treated patients vary depending on data source and patient characteristics, but overall in post marketing reporting (even taking into account recognised limitations of spontaneous data sources), the reporting rate of suicidality is very low. Although the results of the different meta-analyses conducted with duloxetine differ, with one analysis indicating a higher statistical risk than another, the overall trend across the class appears to be in children and in patients younger than 25 years old with psychiatric disorders.
Risk factors and risk groups	Lilly's meta-analyses of placebo-controlled studies with duloxetine suggest that there is a potential but not statistically significantly increased risk of suicidal thinking and behaviour in young adults (aged 18 to 24 years) with duloxetine treatment.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4, 4.8, and 5.1 Section 4.4 advises to monitor and supervise patients for suicidality and not to use in treatment of children and adolescents under the age of 18 years Additional risk minimisation measures: No risk minimisation measures

Important missing information: Prospective data about potential risks of exposure to duloxetine during Pregnancy

Risk minimisation measures	Routine risk minimisation measures: SmPC: 4.6 and 5.3 Section 4.6 advises that duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Additional risk minimisation measures: No risk minimisation measures
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up forms for congenital anomaly and pregnancy outcome. Additional pharmacovigilance activities: F1J-MC-B034 Duloxetine Pregnancy Registry

II.C Xeristar Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Xeristar.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study short name: F1J-MC-B034 Duloxetine Pregnancy Registry

Purpose of the study: To develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and foetal outcomes of women exposed to Duloxetine during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, and any serious adverse pregnancy outcomes. These events will be assessed among the enrolled women throughout the pregnancy. The events will also be assessed among infants through at least the first year of life.