Summary of the risk management plan for Leqvio (inclisiran)

This is a summary of the risk management plan (RMP) for Leqvio. The RMP details how more information will be obtained about Leqvio's risks and uncertainties (missing information).

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

This summary of the RMP for Leqvio should be read in the context of all of this information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

Leqvio is authorised for adults as an adjunct to diet and maximally tolerated statin therapy, for the treatment of primary hypercholesterolaemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C) (see SmPC for the full indication). It contains inclisiran as the active substance and it is administered as a subcutaneous injection.

Further information about the evaluation of Leqvio's benefits can be found in Leqvio's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/leqvio

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Leqvio together with measures to minimize such risks and the proposed studies for learning more about Leqvio's risks, are outlined below.

Measures to minimize 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 minimize its risks.

Together, these measures constitute routine risk minimization 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 pharmacovigilance activities.

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

II.A: List of important risks and missing information

Important risks are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. 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 Leqvio. 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).

Table 1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	Long-term safety
	Use in pregnancy and breast-feeding
	Use in patients with severe hepatic impairment

II B: Summary of important risks

Table 2 Missing information: Long-term safety

Risk minimization measures	Routine risk minimization measures: SmPC Section: None PL Section: None Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study CKJX839A12201E1 (ORION-3), Study CKJX839A12306B (ORION-8) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 3 Missing information: Use in pregnancy and breast-feeding

Risk minimization measures	Routine risk minimization measures: SmPC Section: 4.6 PL Section: 2 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Inclisiran PRegnancy outcomes Intensive Monitoring (PRIM) See Section II.C of this summary for an overview of the post-authorization development plan.

Table 4 Missing information: Use in patients with severe hepatic impairment

Risk minimization measures	Routine risk minimization measures: SmPC Section: 4.2, 5.2 PL Section: 2 Additional risk minimization measures: None

II C: Post-authorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of Leqvio.

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

Table 5 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
CKJX839A12201E1 (ORION-3)	Rationale: ORION-3 study is an open-label, long-term extension study in subjects who completed the Phase II ORION-1 study. Patients in the inclisiran arm will continue on inclisiran (Group1) and patients on placebo will be switched to evolocumab for 1 year and then switched to inclisiran (Group 2). Objective: To further characterize the long term safety and tolerability of inclisiran (AEs, SAEs, Physical examination, CV events (including CV deaths) and laboratory evaluations. To evaluate the long term safety and tolerability of inclisiran (Group 1; inclisiran only arm).
CKJX839A12306B (ORION-8)	Rationale: This extension study allows subjects continued access to inclisiran treatment and to allow the collection of additional efficacy and safety beyond the end of the original studies. Objective: To evaluate the safety and tolerability profile of long term use of inclisiran.

Study short name	Rationale and study objectives
Inclisiran PRegnancy outcomes Intensive Monitoring (PRIM)	PRIM as an additional pharmacovigilance activity is intended to monitor actual use in pregnancy and to proactively collect pregnancy outcomes for reported cases. The overall objective of the inclisiran PRIM program is to collect data on pregnancy outcomes in patients treated with inclisiran during pregnancy or prior to pregnancy (including congenital malformations, spontaneous abortions, stillbirths and other adverse birth outcomes) as well as infant outcomes at 3 and 12 months post-delivery, including breast-feeding status and exposures, neonatal and infant deaths and developmental delays. The findings from this program will be used to evaluate the missing information 'Use in pregnancy and breast-feeding', according to the RMP.