Regulatory Affairs

Leqvio®

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Inclisiran
Product(s) concerned (brand name(s)):	Leqvio
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Summary of the risk management plan for Leqvio (Inclisiran)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Leqvio is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Leqvio in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Leqvio.

I. The medicine and what it is used for

Leqvio is authorised for adults with hypercholesterolaemia [including heterozygous familial hypercholesterolaemia] or mixed dyslipidaemia as an adjunct to diet:

- In combination with a maximally tolerated statin dose with or without other lipid-lowering therapies in patients requiring an additional reduction in low-density lipoprotein cholesterol (LDL C) or
- Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom statins are contraindicated.

The effect of Leqvio on cardiovascular morbidity and mortality has not yet been determined.

It contains inclisiran as the active substance and it is administered as a subcutaneous injection.

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 the prescribing information 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: Prescribing information 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: Prescribing information Section: 'Pregnancy/Breast-feeding' PL Section: 'Pregnancy and breast-feeding' 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: Prescribing information Section: 'Dosage/Administration'; 'Pharmacokinetics' PL Section: 'Warnings and precautions' 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.

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.