Summary of risk management plan for Leflunomide Orion (leflunomide) Orion Corporation

Date: 6.7.2022, Version 1.1

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

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

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

I. The medicine and what it is used for

Leflunomide Orion is authorised for the treatment of active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD) and active psoriatic arthritis (see SmPC for the full indication). It contains leflunomide as the active substance and it is given by mouth.

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

Important risks of Leflunomide Orion, together with measures to minimise such risks and the proposed studies for learning more about leflunomide'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 Leflunomide Orion, 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 continuously and regularly analysed, 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 Leflunomide Orion is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Leflunomide Orion 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 leflunomide. 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	
Important identified risks	Hepatic reactions
	Blood cytopenia
	Severe skin reactions
	Infections
	Interstitial lung disease
	Teratogenicity
	Hypertension
	Concomitant use of other Disease-Modifying Antirheumatic Drugs (DMARDs) (methotrexate)
Important potential risks	Male-mediated foetal toxicity
	Lymphoproliferative disorders
	Progressive multifocal leukoencephalopathy
	Renal failure
	Peripheral neuropathy
	Risk of interaction with CYP2C8 substrates, CYP1A2 substrates, BCRP substrates, OATP1B1/B3 substrates, OAT3 substrates, warfarin and oral contraceptives
Missing information	Use in children
	Concomitant use of biologic DMARDs

II.B Summary of important risks

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

Important identified risk: Hepatic reactions	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.1, 4.2, 4.3, 4.4 and 4.8. PL sections 2 and 4. Alanine aminotransferase (ALT) or serum glutamopyruvate transferase (SGPT) must be checked: • before initiation of leflunomide, • every two weeks during the first six months of treatment, and • every 8 weeks thereafter. Additional risk minimisation measure: Physician leaflet

Important identified risk: Blood cytopenia	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.1, 4.2, 4.3, 4.4 and 4.8. PL sections 2 and 4. Complete blood cell count, including a differential white blood cell count and a platelet count, must be checked: • before initiation of leflunomide, • every two weeks during the first six months of treatment, and • every 8 weeks thereafter Additional risk minimisation measure: Physician leaflet

Important identified risk: Infections	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8. PL sections 2 and 4. Before treatment patients should be screened for latent or active tuberculosis.

Important identified risk: Infections	
	If severe, uncontrolled infections occur, it may be necessary to interrupt leflunomide treatment and administer a wash-out procedure. <u>Additional risk minimisation measure:</u> Physician leaflet

Important identified risk: Teratogenicity	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC sections 4.3, 4.4, 4.6 and 5.3. PL sections 2 and 4. Pregnancy must be excluded before start of treatment with leflunomide. Women of childbearing potential have to use effective contraception during and up to 2 years after treatment. If a waiting period of up to approximately 2 years under reliable contraception is considered unpractical, prophylactic institution of a washout procedure may be advisable. Male patients should be aware of the possible male-mediated foetal toxicity. Reliable contraception during treatment with leflunomide should be guaranteed. <u>Additional risk minimisation measure:</u> Physician leaflet

Important identified risk: Concomitant use of other Disease-Modifying Antirheumatic Drugs (DMARDs) (methotrexate)	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC sections 4.1, 4.4, 4.5 and 5.1. PL sections 2 and 4. Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g., methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects. Switching from leflunomide to another DMARD without following the washout procedure may increase the risk of serious adverse reactions even for a long time after the switching.

Important identified risk: Concomitant use of other Disease-Modifying Antirheumatic Drugs (DMARDs) (methotrexate)	
	Additional risk minimisation measure: Physician leaflet

Important potential risk: Male-mediated foetal toxicity	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4. PL section 2. Male patients should be aware of the possible male-mediated foetal toxicity. Reliable contraception during treatment with leflunomide should be guaranteed. Additional risk minimisation measure: Physician leaflet

II.C Post-authorisation development plan

There are no studies required for Leflunomide Orion.