Summary of risk management plan for Nordimet

This is a summary of the risk management plan (RMP) for:

Nordimet® 7.5 mg solution for injection in pre-filled pen
Nordimet® 10 mg Solution for injection in pre-filled pen
Nordimet® 12.5 mg Solution for injection in pre-filled pen
Nordimet® 15 mg Solution for injection in pre-filled pen
Nordimet® 17.5 mg Solution for injection in pre-filled pen
Nordimet® 20 mg Solution for injection in pre-filled pen
Nordimet® 22.5 mg Solution for injection in pre-filled pen
Nordimet® 25 mg Solution for injection in pre-filled pen

Nordimet 7.5 mg solution for injection in pre-filled syringe
Nordimet 10 mg solution for injection in pre-filled syringe
Nordimet 12.5 mg solution for injection in pre-filled syringe
Nordimet 15 mg solution for injection in pre-filled syringe
Nordimet 17.5 mg solution for injection in pre-filled syringe
Nordimet 20 mg solution for injection in pre-filled syringe
Nordimet 22.5 mg solution for injection in pre-filled syringe
Nordimet 25 mg solution for injection in pre-filled syringe

The RMP details important risks of Nordimet, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information).

The summary of product characteristics (SmPC) of Nordimet and its respective package leaflet give essential information to healthcare professionals and patients on how these products should be used.

This summary of the RMP for Nordimet should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 Nordimet's RMP.

I. The medicine and what it is used for

Nordimet is indicated for (see respective SmPCs for the full indications)

- Active rheumatoid arthritis in adult patients,
- Polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate,
- Severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients.
- Induction of remission in moderate steroid-dependent Crohn's disease in adult patients, in combination with corticosteroids and for maintenance of remission, as monotherapy, in patients who have responded to methotrexate.

Nordimet contains methotrexate as an active substance. Both the prefilled pens and pre-filled syringes are administered subcutaneously. Across all authorised formulations, one ml of solution contains 25 mg of methotrexate.

Further information about the evaluation of Nordimet's benefits can be found in Nordimet'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/nordimet

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

Important risks of Nordimet, together with measures to minimise such risks and the proposed studies for learning more about Nordimet 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 minimization* measures.

For Nordimet, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

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 Nordimet is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Nordimet are risks that need special risk management activities to further investigate or minimise 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 Nordimet . 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	Haematological toxicity
	Hepatotoxicity
	Pulmonary toxicity
	Renal toxicity
	Medication errors due to inadvertent daily instead of once weekly dosing
Important potential risks	None
Missing information	Exposure in children younger than 3 years old

II.B Summary of important risks

Important identified risk: Haematological toxicity	
Evidence for linking the risk to the medicine	**-Post-marketing data (Nordic safety database)** **-Product SmPC** **-Rajnics et al (2017)** **-Rao (2014)**
Risk factors and risk groups	Patients treated with methotrexate.
Risk minimization measures	Routine risk minimization measures Warning in sections 4.4, 4.5 and 4.8 of the SmPC Contraindication in section 4.3 of the SmPC Warning in section 2 and 4 of the PL Restricted medical prescription Additional risk minimization measures: None

Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	**- Conway & Carey (2017)** **- Djurić et al (2017)** **- Pandit et al (2012)** **- Post-marketing data (Nordic safety database)** **- Product SmPC** **- Shen et al (2019)**
Risk factors and risk groups	Patients treated with Methotrexate.
Risk minimization measures	Routine risk minimization measures Warning in sections 4.2, 4.4, 4.5 and 4.8 of the SmPC Contraindication in section 4.3 of the SmPC Warning in section 2 and 4 of the PL Restricted medical prescription Additional risk minimization measures: None

Important identified risk: Pulmonary toxicity	
Evidence for linking the risk to the medicine	**-Albrecht et al (2010)** **-Fragoulis et al (2019)** **-Post-marketing data (Nordic safety database)** **-Product SmPC** **-Skeoch et al (2018)**
Risk factors and risk groups	Patients treated with methotrexate. However, special caution is required in patients with impaired pulmonary function. Particular caution should be exercised in patients with inactive or chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C), due to possible activation.
Risk minimization measures	Routine risk minimization measures Warning in sections 4.4 and 4.8 of the SmPC Warning in sections 2 and 4 of the PL Restricted medical prescription Additional risk minimization measures: None

Important identified risk: Renal toxicity	
Evidence for linking the risk to the medicine	**-Schiff et al (2000)** **-Albrecht et al (2010)** **-Arakawa et al (2018)** **-Post-marketing data (Nordic safety database)** **-Product SmPC**
Risk factors and risk groups	Patients treated with MTX. Special caution is required in patients with impaired renal function. Special caution is also required in patients treated with other drugs which affect the elimination of MTX and thus increase the potential for methotrexate toxicity (e.g proton pump inhibitors, NSAIDS...)
Risk minimization measures	Routine risk minimization measures: Warning in sections 4.2, 4.3, 4.4 and 4.8 of the SmPC Warning in sections 2 and 4 of the PL Restricted medical prescription Additional risk minimization measures: None

Important identified risk: Medication errors due to inadvertent daily instead of once weekly dosing	
Evidence for linking the risk to the medicine	**-Karlen et al (2015)** **-Post-marketing data (Nordic safety database)** **-PRAC Referral procedure (2019)** **-Vial et al (2018)**
Risk factors and risk groups	All patients taking methotrexate. However, patients who have existing hepatic impairment, renal disease, and other organ toxicities are more prone to the adverse effects of medication errors especially if an overdose occurred.
Risk minimization measures	Routine risk minimization measures Boxed warning in section 4.2 of the SmPC Warning in sections 4.4 and 4.8 of the SmPC Warning in sections 2 and 3 of the PL Restricted medical prescription Additional risk minimization measures: DHPC communication

Missing information: Exposure in children younger than 3 years old	
Risk minimization measures	Routine risk communication Limited guidance in sections 4.2 and 4.4 of the SmPC Warning in sections 2 and 3 of the PL Restricted medical prescription 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 required for Nordimet.

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

There are no studies required for either Nordimet.