Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for METHOTREXATE 2.5 mg and 10 mg tablets

This is a summary of the risk management plan (RMP) for METHOTREXATE 2.5 mg and 10 mg tablets with at least one indication requiring treatment once a week (hereinafter referred to as Methotrexate). The RMP details important risks of Methotrexate, how these risks can be minimised, and how more information will be obtained about Methotrexate's risks and uncertainties (missing information).

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

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

I. The Medicine and What It is used for

Methotrexate is authorised for two indications requiring once a week treatment: psoriasis and rheumatoid arthritis in adults (see SmPC for the full indication). It contains Methotrexate as the active substance and it is given orally.

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

Important risks of Methotrexate, together with measures to minimise such risks and the proposed studies for learning more about Methotrexate's risks, if any, 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 Methotrexate, 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, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of Methotrexate 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 Methotrexate. 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 11: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• Medication errors due to inadvertent daily instead of once weekly dosing • Opportunistic infections (e.g. Pneumocystis jirovecii pneumonia) • Lymphomas • Haematological toxicity • Hepatotoxicity • Pulmonary toxicity • Renal toxicity • Gastrointestinal haemorrhage • Nervous system disorders • Leukoencephalopathy, impaired vision • Teratogenicity (abortion and congenital disorders) • Effects on fertility
Important potential risks	• None
Missing information	• None

II.B Summary of Important Risks

Table 12: Summary of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Important identified risk: Medication errors due to inadvertent daily instead of once weekly dosing	
Risk minimisation measures	**Routine risk minimisation measures:** Boxed warning in SmPC section 4.2.

	SmPC section 4.4. SmPC section 4.9 where instructions on overdose management are given. Boxed warning in PL section 3. Pack size: Legal status: Prescription only medicine. Replacement of bottle package with blisters (within 4 years). Warning on inner and outer package **Additional risk minimisation measures:** Healthcare Professional Guide Patient Alert card DHPC

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Methotrexate.

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

There are no studies required for Methotrexate.