13 Part VI: Summary of the risk management plan (RMP) Methotrexate

This is a summary of the RMP for methotrexate, 10 mg/ml and 20 mg/ml, solution for injection in PFS; 100 mg/ml, concentrate for solution for infusion; 2.5 mg, 5 mg and 10 mg, tablets and 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, solution for injection in pre-filled injector. The RMP details important risks of methotrexate solution for injection in PFS, concentrate for solution for infusion, tablets and solution for injection in pre-filled injector, how these risks can be minimized, and how more information will be obtained about methotrexate solution for injection in PFS, concentrate for solution for infusion, tablets and solution for injection in pre-filled injector's risks and uncertainties (missing information).

Methotrexate solution for injection in PFS, concentrate for solution for infusion, tablets and solution for injection in pre-filled injector's summaries of product characteristics (SmPCs) and its package leaflets (PLs) give essential information to healthcare professionals (HCPs) and patients on how methotrexate solution for injection in PFS, concentrate for solution for infusion, tablets and solution for injection in pre-filled injector should be used.

Important new concerns or changes to the current ones will be included in updates of methotrexate solution for injection in PFS, concentrate for solution for infusion, tablets and solution for injection in pre-filled injector's RMP.

13.1 Part VI: I. The medicine and what it is used for

Methotrexate, 10 mg/ml, Solution for injection:
Treatment of different malignant diseases such as Acute lymphoblastic leukemia (ALL) and breast cancer.

Methotrexate, 100 mg/ml, Concentrate for solution for infusion
Methotrexate is indicated in the treatment of different malignant diseases such as ALL, breast cancer and osteosarcoma.

Methotrexate, 2.5 mg, 5 mg and 10 mg, Tablets

- *Antirheumatic:* Active rheumatoid arthritis in adult patients where treatment with disease modifying antirheumatic drugs is indicated.
- Polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA) when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- *Antipsoriatic:* Severe and generalized psoriasis vulgaris, especially plaque-type, in adults which cannot be sufficiently treated with conventional therapy such as phototherapy, psoralen and ultraviolet A (PUVA), and retinoids.
- *Cytostatic:* Maintenance treatment in acute lymphatic leukemia.

Methotrexate, 10 mg/ml , Solution for injection in PFS:

- Active rheumatoid arthritis in adult patients
- Polyarthritic forms of severe, active JIA (children > 3 years) when the response to 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.

Methotrexate, 20 mg/ml, Solution for injection in PFS:

- Active rheumatoid arthritis in adult patients
- Polyarthritic forms of severe, active JIA when the response to 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.

Methotrexate, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, Solution for injection in pre-filled injector

Methotrexate is indicated for the treatment of

- Active rheumatoid arthritis in adult patients.
- Polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to 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.
- Mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines.

It contains methotrexate as the active substance and it is administered via intramuscular (IM), subcutaneous (s.c.) or intravenous (i.v.) route (IM or s.c.in children and adolescents, and i.v. route in adults) in the form of solution for injection in PFS (10 mg/ml and 20 mg/ml), solution for injection (10 mg/ml) and concentrate for solution for infusion (100 mg/ml), solution for injection in pre-filled injector (7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg) or it is given orally in the form of tablets (2.5 mg, 5 mg and 10 mg).

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of methotrexate solution for injection in PFS, solution for injection; concentrate for solution for infusion, tablets and solution for injection in pre-filled injector, together with measures to minimize such 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 PLs and SmPCs addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized 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 the case of methotrexate solution for injection in PFS, solution for injection; concentrate for solution for infusion, tablets and solution for injection in pre-filled injector, 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 analyzed, including periodic safety update report (PSUR) assessment (if applicable) so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance (PhV) activities*.

If important information that may affect the safe use of methotrexate solution for injection in PFS, solution for injection, concentrate for solution for infusion, tablets and solution for injection in pre-filled injector is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of methotrexate solution for injection in PFS, solution for injection, concentrate for solution for infusion, tablets and solution for injection in pre-filled injector are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered/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 solution for injection in PFS, solution for injection, concentrate for solution for infusion, tablets and solution for injection in pre-filled injector. 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 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Opportunistic infections (e.g. *Pneumocystis jirovecii pneumonia*)
	Lymphomas
	Hematological toxicities
	Nervous system disorders (Leukoencephalopathy, impaired vision)
	Pulmonary toxicity
	Gastrointestinal hemorrhage
	Hepatotoxicity
	Renal toxicity
	Teratogenicity (including fetal death and abortion)
	Effects on fertility
	Medication errors due to inadvertent daily instead of once weekly dosing
Important potential risks	None
Missing information	Use in children less than 3 years of age

13.2.2 Part VI – II.B: Summary of important risks

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

Table 13-2 Important identified risk: Medication errors due to inadvertent daily instead of once weekly dosing

Risk minimization measures	**Routine risk communication:** SmPC sections 4.2, 4.4 and 4.9 PL sections 2 and 3 Legal status: Prescription only Package: For tablet formulations of methotrexate containing products for oral use, bottles or tubes used as immediate packaging to be replaced by blisters. **Additional risk minimization measures:** Direct Healthcare Professional Communication (DHPC) Education materials for oral formulations only: • HCP guide • Patient card
Additional Pharmacovigilance activities	**Additional pharmacovigilance activities:** None

13.2.3 Part VI – II.C: Post-authorization development plan

13.2.3.1 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 methotrexate solution for injection in PFS, concentrate for solution for infusion, tablets and solution for injection in pre-filled injector.

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

There are no studies required for methotrexate solution for injection in PFS, solution for injection; concentrate for solution for infusion, tablets and solution for injection in pre-filled injector.