Part VI: Summary of the risk management plan

Summary of risk management plan for methotrexate, Afortastraxat tablets:

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

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

I. The medicine and what it is used for

Afortastraxat is authorised for treatment of active rheumatoid arthritis in adult patients, polyarthritic forms of active, severe juvenile idiopathic arthritis (JIA) in adolescents and children aged 3 years and over when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate, severe, treatment-refractory, disabling psoriasis which does not respond sufficiently to other forms of treatment such as phototherapy, psoralen and ultraviolet A radiation (PUVA) therapy and retinoids, and severe psoriatic arthritis in adult patients and maintenance treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children aged 3 years and over..

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

Important risks of Afortastraxat, together with measures to minimise such risks and the proposed studies for learning more about Afortastraxat's risks, are outlined below.

Measures to minimize the risks identified for medicinal products are:

- 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 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 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 Afortastraxat 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 Afortastraxat. 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	Medication errors due to inadvertent daily instead of once weekly dosing (potential for overdose)
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important identified risk: Medication errors due to inadvertent daily instead of once weekly dosing (potential for overdose)	
Evidence for linking the risk to the medicine	Oral methotrexate is indicated in the treatment of active rheumatoid arthritis, adult psoriasis, severe JIA in adolescents and children over 3 years of age, and in a number of oncological indications such as ALL. Compared to dosing for antineoplastic indications, methotrexate for rheumatological and dermatological diseases is administered once weekly as low-dose therapy. Harmful or fatal errors with low-dose oral methotrexate have been reported; most errors involved accidental daily dosing of oral methotrexate that was intended for weekly administration [EMA/215649/2018, 2018; Grissinger, 2018]. The risk of dosing errors with methotrexate has been recognised for many years and several measures are already in place in some EU countries to reduce this risk, including the use of visual reminders on the medicine packs.
Risk factors and risk groups	A range of factors contribute to these adverse events, including patients not being given sufficient information on how often to take the drug (once weekly and not once daily), lack of clear packaging and variations in patient monitoring and treatment reviews [Mayor, 2003].
Risk minimisation measures	Routine risk m15inimization measures: Section 4.2 of the SmPC states that methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. In addition, section 4.2 of the SmPC includes a boxed warning stating that in the treatment of rheumatological or dermatological diseases, Afortastraxat (methotrexate) must only be taken once a week. Dosage errors in the use of Afortastraxat (methotrexate) can result in serious adverse reactions, including death. It advises to read very carefully the section regarding

	posology of the product. Section 4.2 of the SmPC also states that the prescriber should specify the day of intake on the prescription and that the prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen. There is a warning in section 4.4 of the SmPC stating that the prescriber should make sure patients understand that methotrexate should only be taken once a week. The prescriber should specify the day of intake on the prescription and patients should be instructed on the importance of adhering to the once weekly intakes. In addition, this section includes a boxed warning regarding patients with rheumatological or dermatological diseases, who must be informed unequivocally that treatment is to be taken just once a week and not daily. Incorrect use of methotrexate can result in severe and even fatal adverse reactions. Section 4.9 of the SmPC states that cases of overdose have been reported, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate. Section 2 of the PL includes boxed information about the dosage of methotrexate when used for rheumatological and dermatological diseases and advises to read very carefully the section regarding posology of the product. When used for these indications, the product must only be taken once a week. Taking too much methotrexate may be fatal. Section 3 of the PL indicates that the doctor will decide what dose of methotrexate is needed according to the condition the patient is being treated for, how severe it is and the general health of the patient. This dose should be kept to exactly and the doctor's instructions on when to take the medicine should be followed. This section also includes information about the dosage of methotrexate when used for rheumatological and dermatological diseases and indicates that when used for these indications, the product must only be taken once a week. In addition, section 3 of the PL includes a warning stating that if the patient takes more methotrexate than he should, the recommendations made by the doctor should be followed. The dose is never to be changed based on the decision of the patient. It also advises on the symptoms of an overdose and that the doctor or hospital casualty department should be contacted if it is suspected that too much has been taken. Labelling: warning on packaging. Blister packs only. Restricted medical prescription. Targeted follow-up questionnaires for all medication errors resulting in overdose. Additional risk 16minimization measures: Educational material (including a guide for health care professionals and a patient card).

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 Afortastraxat.

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

There are no studies required for Afortastraxat.