Risk Management Plan Summary

for

METHOTREXATE

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic joint swelling disease of unknown cause. In most of patients with RA, onset often begins with fever, weakness and joint pain. The majority of these occurrence studies curried out in Northern European and North American areas estimate the occurrence of about 0.5 – 1.1%. Studies from Southern European countries report a frequency of 0.3–0.7%. Studies from developing countries also report a relatively lower occurrence of the disease (between 0.1% and 0.5%). The annual occurrence rates of RA vary between 20 and 50 cases per 100,000 individual in North American and North European countries. There are only few studies from Southern European countries indicating a relatively lower occurrence of the disease.

Although the cause of rheumatoid arthritis (RA) is still unclear, it may include genetic and environmental factors in the disease as the disease mechanism.

Juvenile idiopathic arthritis (JIA)

Although inflammation of joint in children (Juvenile idiopathic arthritis) is defined as inflammation of joint beginning before age 16 years, the age at onset is often much lower, with the highest frequency occurring in children aged 1-3 years. This is more common in females.

The overall prevalence is estimated to be 1-2 per 1,000 children, with an incidence of 1 per 10,000.A study from Germany found an occurrence rate of 20 cases per 100,000 populations, with an incidence rate of 3.5 cases per 100,000 populations. Estimates from Norway include a occurrence rate of 148 cases per 100,000 population with an incidence rate of 22 cases per 100,000 population. The incidence of JIA in Japan has been reported to be low. Disease-associated mortality for JIA is difficult to quantify, but it is estimated to be less than 1% in Europe and less than 0.5% in North America.

Psoriasis

Psoriasis is an inflammatory disease that involves higher rate of cells generation that produced keratin (the key structural material making up the outer layer of human skin), with an increase in the epidermal cell turnover rate. Environmental, genetic, and immunologic factors appear to play a role. The disease most commonly manifests on the skin of the elbows, knees, scalp, Low back areas, between hips, and front end of penis. In up to 30% of patients, the joints are also affected. Overall, approximately 2-3% of people are affected by psoriasis worldwide. Psoriasis can begin at any age. Approximately 10-15% of new cases begin in children younger than 10 years. The median age at onset is 28 years.

Psoriasis appears to be slightly more prevalent among women than among men; however, men are thought to be more likely to experience the eye disease.

The incidence of psoriasis is dependent on the climate and genetic heritage of the population. It is less common in the tropics and in dark-skinned persons. Psoriasis prevalence in African Americans is 1.3% compared with 2.5% in whites.

Crohn's disease

Crohn's disease is a swelling of the digestive system that can affect any part of the tract from the mouth to the anus. Individuals with this condition often experience periods of symptomatic relieve and re-occurrence.

Crohn's disease is reported to be more common in white patients than in black patients and rare in Asian and Hispanic children.

The rate of Crohn's disease is 1.1-1.8 times higher in women than in men. This pattern is reversed with pediatric, which has a higher incidence in boys than in girls (pediatric male-to-female ratio, ~1.6:1).

The age of onset of Crohn's disease has a two peak: the first peak occurs between the ages of 15 and 30 years (late adolescence and early adulthood), and the second occurs mainly in women between the ages of 60 and 70 years. However, most cases begin before age 30 years, and approximately 20-30% of all patients with Crohn's disease are diagnosed before age 20 years.

VI.2.2 Summary of treatment benefits

Methotrexate is indicated for the treatment of active rheumatoid arthritis (inflammation of joint) in adult patients, severe joint pain or inflammation of unknown cause in children, when the response to pain-killing and fever reducing drugs (nonsteroidal anti-inflammatory drugs (NSAIDs)) has been inadequate, severe non responsive disabling scaly skin rash (psoriasis), which is not adequately responsive to other forms of therapy such as phototherapy, ultra-violet light (PUVA), and vitamin A chemical compounds (retinoids), and severe psoriatic arthritis in adult patients and mild to moderate infection of any part of gastrointestinal tract (Crohn's disease) either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines.

As per the literature published by To H and colleagues, Methotrexate (MTX) is the most important drug for treating rheumatoid arthritis dosing at bedtime improve the arthritis symptoms. Emery P and colleagues mentioned that improvement as well as non-progression of rheumatoid arthritis was achieved by combined treatment of etanercept plus methotrexate. Céspedes-Cruz A and colleagues mentioned methotrexate treatment produced a significant improvement across a wide range of health related quality of life components in the patients with juvenile idiopathic arthritis.

Shaker OG and colleagues mentioned that methotrexate is more effective than psoralen and ultraviolet light A to treat psoriasis.

Uhlen S and colleagues mentioned that methotrexate is effective and safe in the treatment of paediatric Crohn's disease. Lémann M and colleagues concluded that there is a long-term benefit of maintenance treatment with methotrexate in patients with chronically active Crohn's disease, with side effects that are usually only moderate.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of methotrexate in children less than 3 years of age has not been established.

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	**What is known**	**Preventability**
Medication error/dose related toxicity	Methotrexate to be injected once weekly. Methotrexate solution for injection is given by subcutaneous route. Methotrexate may be injected intramuscularly (in a muscle), intravenously (in a vein) or subcutaneously (under the skin). When methotrexate is given by the intramuscular route, local undesirable effects (burning sensation) or damage (formation of sterile abscess, destruction of fatty tissue) at the site of injection can occur commonly. As there is very little data about giving the medicine intravenously in children and adolescents, it must only be injected under the skin or into a muscle.	Yes This medicine should be administered by or under the supervision of physician or healthcare professional. It is advisable to determine a fixed, appropriate weekday as day of injection. The patient should be explicitly informed about once weekly administration. In certain cases your doctor may decide to instruct you how to inject this medicine under the skin yourself. You will then receive appropriate training. Under no circumstances should you try to inject yourself before you have received such training. The patient should inform physician or pharmacist in case of any adverse event. The patient should not use more methotrexate than prescribed by doctor and do not take double dose to make up for a forgotten dose. If stop

Risk	What is known	Preventability
		using this medicine, then talk to doctor immediately.
Liver toxicity (hepatic impairment/ hepatotoxicity)	Methotrexate can cause chronic liver damage (liver cirrhosis), formation of scar tissue of the liver (liver fibrosis), fatty degeneration of the liver [all uncommon - may affect up to 1 in 100 people], inflammation of the liver (acute hepatitis) [rare - may affect up to 1 in 1,000 people] and liver failure [very rare - may affect up to 1 in 10,000 people]	Yes Do not use this medicine if you are suffering from any liver disease. Before starting the therapy test should be carried out for liver function, serum albumin (a protein in the blood). Treatment should not be instituted or should be discontinued if any abnormality of liver function tests, or liver biopsy, is present or develops during therapy. Due to its potentially toxic effect on the liver, additional liver damaging medicinal products should not be taken during treatment with methotrexate unless clearly necessary and the consumption of alcohol should be avoided or greatly reduced. Tell your doctor immediately

Risk	What is known	Preventability
		if you experience any of the symptoms, as these may indicate a serious, potentially life-threatening side effect, which require urgent specific treatment.
Kidney disease (renal impairment)	Methotrexate may caused kidney damage with symptoms such as swelling of the hands, ankles or feet or changes in frequency of urination or decrease or absence of urine; these may be signs of kidney failure [rare - may affect up to 1 in 1,000 people]	Yes Do not use this medicine if you are suffering from any kidney disease. Before starting the treatment with methotrexate, kidney function test should be carried out. Where kidney function may be compromised (e.g. in the elderly), monitoring should take place more frequently. This applies in particular, when medicinal products are administered concomitantly, which affect the elimination of methotrexate, cause kidney damage (e.g. non-steroidal anti-inflammatory medicinal products) or which can potentially lead to impairment of blood formation.

Risk	What is known	Preventability
		Tell your doctor immediately if you experience any of the symptoms, as these may indicate a serious, potentially life-threatening side effect, which require urgent specific treatment.
Suppression of body immune system (Immunosuppression/ Immunotoxicity)	Methotrexate may have effect on immune system and affect the results of immunological tests (test carried out to check body immune system)	Yes Do not use this medication if you are suffering from any disease which affects immune system. Tell your doctor immediately if you experience any of the symptoms, as these may indicate a serious, potentially life-threatening side effect, which require urgent specific treatment.
Gastrointestinal toxicity	Methotrexate may cause severe diarrhoea, blood in vomiting and black or tarry stool; these symptoms may indicate rare severe complications of gastrointestinal symptoms. e.g. gastrointestinal ulcers. Severe bleeding and dilated colon may affect up to 1 in 10,000 people.	Yes Do not use this medicine if you are suffering from stomach ulcer or intestinal ulcer. Tell your doctor immediately if you experience any of the symptoms, as these may indicate a serious, potentially

Risk	What is known	Preventability
		life-threatening side effect, which require urgent specific treatment.
Lung toxicity (pulmonary toxicity)	Methotrexate may cause dry, non-productive cough, shortness of breath and fever. Inflammation of the lungs (pneumonia) [common - may affect up to 1 in 10 people], Lung fibrosis, shortness of breath and bronchial asthma, accumulation of fluid in the sac around the lung [Rare - may affect up to 1 in 1,000 people]	Yes During therapy lung function test should be performed, if necessary. Patient should inform the doctor for dry, non-productive cough, shortness of breath and fever with methotrexate.
Blood toxicity (Hematotoxicity)	The most relevant undesirable effect is blood cells suppression (Haemopoietic suppression). Overdose may affect blood cell production (haematopoietic) system.	Yes Do not use this medicine if you are suffering from any blood disease. Before starting the treatment, blood samples will be taken in order to check the availability of enough blood cells. Complete blood count with differential blood count and platelets. Bone marrow suppression caused by methotrexate may occur abruptly and with apparently safe dosages. Any profound

Risk	What is known	Preventability
		drop in white-cell or platelet counts indicates immediate withdrawal of the medicinal product and appropriate supportive therapy. Patients should be advised to report all signs and symptoms suggestive of infection.
Pregnancy and breast-feeding (Administration during pregnancy and lactation)	Methotrexate is contraindicated (not advised) during pregnancy. Methotrexate has been shown to be teratogenic (causing deformity to fetus) in humans; it has been reported to cause foetal death and/or congenital abnormalities (abnormalities prior to birth) Methotrexate is excreted in milk in such concentration that there is a risk for infant.	Yes Do not use this medication if you are pregnant or breast-feeding. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Breast-feeding should be stopped prior to and during this treatment. Men and women should exercise effective method for birth-control during treatment and further till six month after discontinuation of treatment.
Damage to the brain or peripheral nervous	Encephalopathy (a brain disorder)/ leukoencephalopathy (a special	Yes

Risk	What is known	Preventability
system (Neurotoxicity)	disorder of the white brain substance) have been reported in cancer patients receiving methotrexate therapy. [Not known: frequency cannot be estimated from the available data] Treatment with methotrexate may cause adverse reactions affecting the central nervous system like tiredness, dizziness. [uncommon: may affect up to 1 in 100 people].Thus ability to drive vehicle and/or operate machines may be compromised and also cause loss of strength or sensation of numbness or tingling in arms and legs, changes in taste (metallic taste), convulsion and paralysis [very rare - may affect up to 1 in 10,000 people]	Tell your doctor immediately if you experience any of the symptoms, as these may indicate a serious, potentially life-threatening side effect, which require urgent specific treatment.
Skin disease (Skin and subcutaneous tissue disorders)	Methotrexate may cause rash, reddening of skin, itching [common - may affect up to 1 in 10 people], increased pigmentation of nails, inflammation of cuticles, furunculosis (deep infection of hair follicles) [very rare - may affect up to 1 in 10,000 people] Methotrexate may also cause severe skin rash or blistering of the skin	Yes Tell your doctor immediately if you experience any of the symptoms, as these may indicate a serious, potentially life-threatening side effect, which require urgent specific treatment.

Risk	What is known	Preventability
	(this can also affect mouth, eyes and genitals); this sign may be very rare[may affect up to 1 in 10,000 people] conditions called Steven Johnson syndrome or burned skin syndrome (toxic epidermal necrolysis). Only mild local skin reactions (such as burning sensations, erythema, swelling, discolouration, severe itching, pain) were observed during therapy. Radiation induced dermatitis and sun-burn can reappear under methotrexate therapy (recall-reaction).	

Important potential risk:

Risk	What is known
Infertility	Methotrexate affects spermatogenesis (creation of sperm) and oogenesis (creation of an ovum) during the period of its administration which may result in decreased fertility. These effects appear to be reversible on discontinuing therapy. As methotrexate can be genotoxic (change or damage genes), all women who wish to become pregnant are advised to consult a genetic counselling centre, if possible, already prior to therapy, and men should seek advice about the possibility

Risk	What is known
	of sperm preservation before starting therapy.
Accidental exposure/ contact with skin	Methotrexate should not come into contact with the surface of the skin or mucosa. In the event of contamination, the affected area must be rinsed immediately with plenty of water.
Use in elderly patients	Dose reduction should be considered in elderly patients due to reduced liver and kidney function as well as lower folate reserves which occur with increased age.

Missing information:

Risk	What is known
Use in children < 3 years of age	Due to insufficient data available for methotrexate use in children < 3 years of age, it is not recommended in children < 3 years of age.

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No studies planned.

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concern	Comment
6.0	12 April 2016	No changes in safety concerns	SmPC and PIL have been revised (product name, procedure number and pharmaceutical form terminology, etc) based upon validation comments received from UK.
5.0	22 January 2016	No changes in safety concerns	Methotrexate 50 mg/ml Pre-filled syringe' is approved under SE/H/1431/01/DC. Details of Methotrexate 50 mg/ml solution for injection in self dose injector included as line extension.
4.0	16 September 2015	Following important identified risk are deleted- • Cardiovascular disorders • Eye disorders • Drug interaction with alcohol, hepatotoxic, hematotoxic medicinal products, NSAIDs, etc.	RMP has been updated as per RMS Day 180 Draft Assessment Report, dated 01-Sep-2015

Version	Date	Safety Concern	Comment
3.0	05 August 2015	Following important identified risk are added- • Cardiovascular disorders • Neurotoxicity • Eye disorders • Skin and subcutaneous tissue disorders • Drug interaction with alcohol, hepatotoxic, hematotoxic medicinal products, NSAIDs, etc.	RMP has been updated as per Day 145 comments received from Hungary.
2.0	29 January 2015	Safety concerns were updated based upon RMS Day 70 Preliminary Assessment Report. **Important identified risk:** • Medication error / dose related toxicity • Hepatic impairment / hepatoxicity • Immunosuppression / Immunotoxicity • Gastrointestinal toxicity • Pulmonary toxicity • Hematotoxicity • Administration during pregnancy and lactation	RMP has been updated as per RMS Day 70 Preliminary Assessment Report

Version	Date	Safety Concern	Comment
		Important potential risk: • Infertility • Accidental exposure / contact with skin • Use in elderly patients **Missing information:** • Use in children under 3 years of age	