VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Rheumatoid arthritis[1]

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 carried 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.

Psoriasis[2]

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. Psoriasis appears to be slightly more prevalent among women than among men. 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.

Acute lymphocytic leukaemia (a type of blood cell cancer)

[1] Alamanos Y, Voulgari PV, Drosos AA. Rheumatoid arthritis in Southern Europe: epidemiological, clinical, radiological and genetic considerations. Current Rheumatology Reviews. 2005 Jan 1;1(1):33-6.
[2] Psoriasis: Practice Essentials, Background, Pathophysiology [Internet]. Emedicine.medscape.com. 2017. Available from: http://emedicine.medscape.com/article/1943419-overview#a1

Acute lymphocytic leukemia (ALL) is uncommon in adults. About 10,000 new cases are diagnosed in adults in Europe each year. In adults, ALL represents about 15% of leukemias: the chronic form is five times more common. ALL affects white more than blacks, males more than females, and those in Western, affluent countries more than those in the developing countries. The number of new cases/year in Europe was 1.3 per 100,000 in men and 0.9 in women. In adults aged 15 and over, half the cases is under age 50, and ALL is rare over the age of 70. ALL is the most common malignancy in children, accounting for 30% of all cancers and 80% of all leukemias. In children almost two-thirds of the cases occur in age from 2 to 6 years.

Leukemia accounts for 30% of all cancers diagnosed in children less than 15 years of age in industrialized countries. Common risk factors for ALL include genetic disorders and exposures to viruses as well as radiation, chemical, or other occupational hazards and previous chemotherapy.[3]

VI.2.2 Summary of treatment benefits

Methotrexate is indicated for the treatment of active rheumatoid arthritis (inflammation of joint) in adult patients, severe non responsive disabling scaly skin rash (psoriasis), and cancer chemotherapy.

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.

Methotrexate (MTX) is one of the treatment options for psoriasis and can be administered both as monotherapy and in combination with other treatments. Shaker OG and colleagues mentioned that methotrexate is more effective than psoralen and ultraviolet light A to treat psoriasis.

[3] Incidence of childhood leukaemia, an ENHIS fact sheet [Internet]. http://www.euro.who.int. 2017. Available from: http://www.euro.who.int/__data/assets/pdf_file/0005/97016/4.1.-Incidence-of-childhood-leukaemia-EDITED_layouted.pdf

Methotrexate is useful as a maintenance therapy in acute lymphoblastic leukemia. Methotrexate inhibits dihydrofolate reductase, resulting in inhibition of deoxyribonucleic acid (DNA) synthesis, repair, and cellular replication. Study (Abromowitch M et. al) results suggested that high-dose methotrexate-based therapy, would be most effective in patients with a presenting leukocyte count of less than 25 x 10^9/L. Study (Wen J et. al) results suggested that metronomic administration of low-dose methotrexate presented significant effects in treating relapsed and refractory non-Hodgkin's lymphoma.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of methotrexate in paediatric population for other than cancer chemotherapy indications are not established.

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	**What is known**	**Preventability**
Liver toxicity (hepatic impairment/ hepatotoxicity)	Methotrexate may cause liver damage (seen as yellowing of the skin and whites of eyes) and raised liver enzymes.	Do not use this medicine if you are suffering from any liver disease. Tell your doctor before taking this medicine if you have /had any liver disease. Before starting this medicine and during treatment, your doctor may carried out blood test, and also to check how well your kidney and liver working. Your doctor may stop methotrexate if you have abnormal liver functions

Risk	**What is known**	**Preventability**
Kidney disease (renal impairment)	Methotrexate may cause kidney damage, blood in urine or stools, pain or difficulty in passing urine, the need to pass urine more than usual	Tell your doctor or pharmacist before taking methotrexate if you have any mild or moderate kidney disease. Do not use this medicine if you have severe kidney problems, including conditions requiring kidney dialysis. Before starting this medicine and during treatment, your doctor may carried out blood test, and also to check how well your kidney working.
Suppression of body immune system/Immune system toxicity (Immunosuppression/ Immunotoxicity)	Methotrexate may reduce body immunity of patients. Due to its effect on immune system, lower the vaccination effect.	Do not use this medication if you are suffering from any disease which affects immune system. Tell your doctor or pharmacist, if you have received any vaccinations recently as methotrexate can reduce their effect.
Gastrointestinal toxicity	Methotrexate may cause stomach pains, soreness of the mouth, throat and lips and black or tarry stools. Gastrointestinal side effects are seen in methotrexate overdose.	Talk to your doctor or pharmacist before taking this medicine if you have gastro-intestinal (digestive) problems. Tell your doctor or pharmacist if you are taking, have recently taken

Risk	**What is known**	**Preventability**
	Methotrexate should be used with extreme caution in patients with gastrointestinal disease.	or might take any other medicines such as aspirin, ibuprofen, indometacin (NSAID's, non-steroidal anti-inflammatory drugs) which are used for pain or inflammation as the effect of Methotrexate Tablets may be altered when they are taken at the same time. Your doctor may stop your methotrexate treatment.
Lung toxicity (pulmonary toxicity)	Methotrexate may cause diseases of lungs like excess fluid between the lungs and chest wall or abdominal swelling (ascites), develop a persistent cough or develop shortness of breath as it may be associated with serious lung disease.	Tell your doctor if you have problems with your lung functions. Your doctor may stop your methotrexate treatment and ask you for investigations like blood test and X-Ray, etc.
Blood toxicity (Hematotoxicity)	Methotrexate may cause abnormal red blood cell function, low levels of white and red blood cells and clot blood cells.	Do not use this medicine if you have any serious blood problems, including severe low red blood cell count (anaemia) and clotting problems. Your doctor may regularly ask you for blood test during methotrexate treatment to check your blood cells.

Risk	What is known	Preventability
Ability to cause birth defects (teratogenicity)	Methotrexate may cause genetic mutation (changes in the gene). Methotrexate can affect sperm and egg product with the potential to cause birth defects.	Do not use this medication if you are pregnant or breast-feeding. If you are pregnant or breast-feeding, think you may become pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Men and women should avoid conception (becoming pregnant or fathering children) during treatment and for at least three months after your treatment with methotrexate has stopped.

Important potential risk:

Risk	What is known
Inability to reproduce children (Infertility)	Methotrexate can decrease fertility. This means that the medicine may cause genetic mutation (changes in the gene). Methotrexate can affect sperm and egg product with the potential to cause birth defects. This effect appears to be reversible after discontinuation of therapy.
Use in elderly patients	Elderly patients may need smaller doses of methotrexate. Methotrexate will be used with extreme caution in elderly patients and the dosage may need to be reduced.
Medication error	Methotrexate dose and frequency are different for different indications. This medicine is taken once a week for

Risk	What is known
	rheumatoid arthritis (chronic joint swelling disease) and psoriasis (scaly skin rash), while generally taken as daily for cancer chemotherapy. For cancer chemotherapy, dose is usually calculated based on various factors e.g. the patient's general health, body surface area and the type of disease.
Damage or inflammation of the white matter of the brain at multiple locations that get worse with time (Progressive multifocal leukoencephalopathy (PML))	Encephalopathy/Leukoencephalopathy (damage to the brain) has been reported in oncologic (cancer) patients receiving methotrexate therapy and cannot be excluded for methotrexate therapy in non-oncologic indications.

Missing information:

Risk	What is known
Use in children for non-cancer indications (Use in paediatric population for non-neoplastic indications)	Not recommended for use in children. Safety and effectiveness in children have not been established, other than in cancer chemotherapy. There are currently no efficacy and safety data available to make any specific recommendations for conditions other than cancer chemotherapy in children.

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
5.0	14 Jul 2017	No change in safety concerns	RMP has been updated as per Mutual recognition Procedure Day 68 assessment report of methotrexate (IE/H/477/001-002/MR).
4.0	22 Jun 2017	Important potential risk 'Progressive multifocal leukoencephalopathy (PML)' has been added	RMP has been updated as per RMS (IE) assessment report.
3.0	19 Oct 2016	No changes in the safety concerns of this RMP.	RMP has been updated for the MRP submission. Changes in product information were done based on agency's recommendation/queries during IE national procedure assessment and

			relevant section of the RMP has been updated.
2.0	18 Aug 2015	The identified risk 'infant/neonatal toxicity after administration during pregnancy and lactation' is amended to 'teratogenicity'. "Medication error" is added as important potential risk	RMP has been updated based upon comments received from HPRA.