VI.2 Elements for a Public Summary

Methotrexate is indicated for:

- Active rheumatoid arthritis in adult patients

- Severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, psoralene-ultraviolet A (PUVA), and retinoids, and severe psoriatic arthritis in adult patients.

- Maintenance therapy in acute lymphoblastic leukemia (ALL)

VI.2.1 Overview of disease epidemiology

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a common chronic inflammatory autoimmune disease characterised by an inflammation of the synovial joints leading to joint and periarticular tissue destruction, as well as a wide variety of extra-articular features. RA is associated with significant morbidity, including pain and disability. Prevalence ranges from 0.5-1.5% of the population in industrialised countries. The incidence of the condition is low, with around 1.5 men and 3.6 women developing RA per 10 000 people per year. The overall occurrence of RA is two to four times greater in women than in men. The peak age of incidence in for both genders is the 70s, but people of all ages can develop the disease.

Psoriasis

Psoriasis is a common, chronic, relapsing, inflammatory skin disorder with a strong genetic basis. The prevalence of psoriasis is estimated to be about 1.3-2.2%, with the highest prevalence being in white people. Men and women are equally affected. It can occur at any age but the majority of cases first present before the age of 35 years. It is uncommon in children. Plaque psoriasis accounts for 90% of all people with psoriasis. Joint disease is associated with psoriasis in a significant proportion of patients (reported in one study to be 13.8%). Psoriasis is associated with Psoriatic arthritis - a seronegative inflammatory arthritis, which between 7-40% of people with psoriasis will develop.

Acute lymphoblastic leukemia

Acute lymphoblastic leukemia is a type of cancer of the blood and bone marrow — the spongy tissue inside bones where blood cells are made affecting the white blood cells, called the lymphocytes. The disease progresses rapidly and creates immature blood cells, rather than mature ones. It is the most common type of cancer in children and accounts for 26% of all cancers in children up to 14 years of age, and for 75% of paediatric leukemia cases. The signs and symptoms may include bleeding from the gums, bone pain, fever, frequent infections, frequent or severe nose-bleeds, lumps caused by swollen lymph nodes in and around the neck, underarm, abdomen or groin, pale skin, shortness of breath, and weakness, fatigue or a general decrease in energy.

VI.2.2 Summary of treatment benefits

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a common chronic inflammatory autoimmune disease. Suppression of inflammation in the early stages of the disease can result in substantial improvements in long-term outcomes. Improvements in the use of existing disease-modifying drugs are important in reducing morbidity and mortality from RA.

Psoriasis

Methotrexate is useful for severe recalcitrant disabling psoriasis not adequately responsive to other forms of therapy such as phototherapy,PUVA, and retinoids, and severe psoriatic arthritis in adult patients. Methotrexate controls the psoriasis process of increased proliferation of epithelial cell production in the skin.

Acute lymphoblastic leukemia

Methotrexate is useful as a maintenance therapy in ALL. Methotrexate inhibits dihydrofolate reductase, resulting in inhibition of deoxyribonucleic acid (DNA) synthesis, repair, and cellular replication.

VI.2.3 Unknowns relating to treatment benefits

The use of methotrexate is not recommended in children below 3 years of age due to insufficient data on efficacy and safety of methotrexate in this group of population.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Medication error/dose related toxicity	Methotrexate for the therapy of rheumatoid arthritis or psoriasis must only be used **once weekly**. Faulty dosing may lead to serious adverse effects including fatal courses. Overdose symptoms may include easy bruising or bleeding, unusual weakness, mouth sores, nausea, vomiting, black or bloody stools, coughing up blood or vomit that looks like coffee grounds, and decreased urinating.	The patients should always take methotrexate exactly as asked by the doctor or pharmacist. Patients should be clearly informed that in rheumatoid arthritis or psoriasis methotrexate must be administered **once weekly**. It is recommended to specify a certain day of the week as “the day for taking Methotrexate” on the prescription. Occurrence and severity of undesirable effects depend on dosage level and frequency of methotrexate method of administration and duration of exposure. However, as severe adverse reactions may occur even at lower doses, it is indispensable that the doctor monitors patients regularly at short intervals. Most undesirable effects are reversible if recognised early. If adverse reactions occur, the dose should be reduced or therapy discontinued and necessary corrective therapeutic measures undertaken, such as administration of calcium folinate. Different tablet strengths have

Risk	What is known	Preventability
		different shapes and markings on the tablets. In addition strengths are also marked in the package with different colors.
Liver impairment/liver toxicity (Hepatotoxicity)	Methotrexate has potentially toxic effects on liver. Regular alcohol consumption and administration of additional liver toxic medicinal products increase the probability of toxic liver effects of methotrexate.	Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially if due to alcohol. Methotrexate must not be used, if the patient has severe liver insufficiency. Liver enzymes, bilirubin and serum albumin should be monitored before starting the therapy. If clinically indicated hepatitis should be excluded. Monitoring of the liver function during the therapy. In case of constant increase in liver enzymes, a reduction of the dose or discontinuation of therapy should be taken into consideration. Patients taking potentially liver toxic medicinal products during methotrexate therapy (e.g. leflunomide, and retinoids) should be closely monitored for possibly increased liver toxicity. Alcohol consumption should be avoided during treatment with methotrexate.
Kidney impairment (Renal and urinary toxicity)	As methotrexate is eliminated mainly through kidneys, increased methotrexate concentrations in serum are to be expected in case of kidney insufficiency, which may result in severe undesirable effects.	Methotrexate should be used with caution in patients with impaired kidney function and dose should be adjusted. Methotrexate must not be used, if the patient has severe kidney insufficiency. Kidney function should be monitored before and during the therapy.

Risk	What is known	Preventability
		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. Dehydration may also intensify the toxicity of methotrexate so it is important to drink enough fluids.
Immunosuppression/ Immunotoxicity	Immunosuppression, sepsis, opportunistic infections (may be fatal in some cases) and shingles (herpes zoster) are listed as possible methotrexate adverse drug reactions. Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case, therapy must be discontinued.	Methotrexate must not be used, if the patient has serious, acute or chronic infections, such as tuberculosis and HIV. During methotrexate therapy concurrent vaccination with live vaccines must not be carried out. Patients should be advised to report all signs and symptoms suggestive of infection.
Alimentary canal toxicity	Diarrhoea and ulcerative stomatitis (mouth inflammation with sores) can be toxic effects and require interruption of the therapy, otherwise haemorrhagic (bleeding) enteritis (inflammation of the intestine) and death from intestinal perforation may occur.	Doctor needs to be contacted as soon as possible and treatment discontinued if patient has sores in mouth or diarrhoea.
Lung toxicity	Acute or chronic interstitial pneumonitis (lung inflammation), often associated with blood eosinophilia (high amount of certain type of white blood cells), may occur and deaths have been reported. Symptoms typically include dyspnoea (shortness of breath),	Before beginning methotrexate therapy or re-instituting methotrexate therapy after a rest period chest x-ray is recommended.. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop

Risk	What is known	Preventability
	cough (especially a dry non-productive cough) and fever for which patients should be monitored at each follow-up visit. Lung/respiratory symptoms require a quick diagnosis and discontinuation of methotrexate therapy. Pneumonitis can occur at all dosages.	persistent, dry, irritating cough, general illness, shortness of breath, chest pain, fever. Methotrexate should be withdrawn from patients with lung symptoms and a thorough investigation should be made to exclude infection. If methotrexate induced lung disease is suspected, treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.
Blood toxicity	Suppression in blood cell formation caused by methotrexate may occur abruptly and with apparently safe dosages. Under (pre-)treatment with substances that may have adverse reactions affecting the bone marrow (e.g.sulfonamides, trimethoprim/sulfamethoxazole, chloramphenicol, pyrimethamine), the risk of pronounced blood cell forming disorders during methotrexate therapy must be considered. The combined use of methotrexate and leflunomide may increase the risk for pancytopenia (general lack of blood cells).	Any profound drop in white cell or platelet counts indicate immediate withdrawal of the medicinal product and appropriate supportive therapy. Methotrexate must not be used if the patient has pre-existing blood disorders, such as incompletely developed bone marrow (bone marrow hypoplasia), lack of platelets or white blood cells, or significant anaemia. Before beginning methotrexate therapy or re-instituting methotrexate therapy after a rest period and during therapy, complete blood count with differential blood count and platelets should be taken. Simultaneous use of other blood toxic medicinal products (e.g. leflunomide) should be avoided.
Administration during pregnancy and lactation	Methotrexate causes embryotoxicity, abortion and foetal defects in humans. In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (first three months of pregnancy). Methotrexate has been shown to be teratogenic to humans; and can cause birth defects, harm unborn babies or cause miscarriages.	Methotrexate must not be used during pregnancy and breast-feeding. If use during the lactation period should become necessary, breast-feeding is to be stopped prior to treatment. Possible risks of effects on reproduction should be discussed with patients of childbearing potential. In women of child-bearing age,

Risk	What is known	Preventability
	Methotrexate passes into breast milk and may cause toxicity in nursing infants.	any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test, prior to initiating therapy. Women must not get pregnant during methotrexate therapy and patients of sexually mature age (women and men) must use effective contraception during treatment with Methotrexate and at least six months thereafter. If, nevertheless, pregnancy occurs during this period, medical advice should be given regarding the risk of harmful effects on the child associated with treatment.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Infertility	Methotrexate has been reported to cause impairment of fertility, abnormally low sperm count (oligospermia), menstrual dysfunction, and absence of menstruation (amenorrhoea), during and for a short period after cessation of therapy.
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 increasing age.

Missing information

Risk	What is known
Use in children below 3 years of age	Use in children below 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a 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. The SmPC and the PL for Methotrexate can be found in the national authority's web page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

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

Not applicable.