VI.2 Elements for a Public Summary

Methotrexate is indicated for

- Active rheumatoid arthritis in adult patients where treatment with disease modifying antirheumatic drugs (DMARD) is indicated.

- Polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA), when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate.

- Severe forms of psoriasis vulgaris, particularly of the plaque type, which cannot be sufficiently treated with conventional therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis.

VI.2.1 Overview of disease epidemiology

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 the for both genders is the 70s, but people of all ages can develop the disease.

Juvenile idiopathic arthritis (JIA) is defined as joint inflammation presenting in children under the age of 16 years and persisting for at least six weeks, with other causes excluded.

The overall prevalence is estimated to be 1-2 per 1,000 children, with an incidence of 1 per 10,000. It is more common in females, although there are differences depending on the subset. It is described in all geographical areas but with large variations.

Psoriasis vulgaris 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.

VI.2.2 Summary of treatment benefits

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.

In juvenile idiopathic arthritis (JIA), untreated chronic inflammation can lead to growth failure or abnormality, osteoporosis and delayed puberty.

Methotrexate is the first choice of systemic agent for people with psoriasis who fulfil the criteria for systemic therapy except that ciclosporin should be offered as the first choice of systemic agent for people who need rapid or short-term disease control (eg, a psoriasis flare), have palmoplantar pustulosis, or are considering conception (both men and women) and systemic therapy cannot be avoided.

Methotrexate is useful for extensive chronic plaque psoriasis in patients who are inadequately controlled by topical therapy alone, or where there is concomitant psoriatic arthropathy. Methotrexate can cause a clinically significant rise in transaminases and long-term therapy may be associated with liver fibrosis.

VI.2.3 Unknowns relating to treatment benefits

The treatment benefits of Methotrexate are well established.

References:

Adib N, Silman A, Thomson W; Outcome following onset of juvenile idiopathic inflammatory arthritis: I. frequency of different outcomes. Rheumatology (Oxford). 2005 Aug;44(8):995-1001. Epub 2005 Apr 12.

Petty RE, Southwood TR, Manners P, et al; International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004 Feb;31(2):390-2.

Psoriasis, NICE Clinical Guideline (Oct 2012)

Rheumatoid arthritis: the management of rheumatoid arthritis in adults, NICE Clinical Guideline (February 2009)

Oen K, Malleson PN, Cabral DA, et al; Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort. J Rheumatol. 2002 Sep;29(9):1989-99.

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 rheumatic or skin diseases must only be used **once weekly.** Faulty dosing may lead to serious adverse effects including fatal courses. Doses exceeding 20 mg/week can be associated with significant increase in toxicity, especially bone marrow suppression.	Patients have to be clearly informed that Methotrexate must be administered **once weekly.** It is recommended to specify a certain day of the week as "day for injection". Occurrence and severity of undesirable effects depend on dosage level and frequency of methotrexate administration. 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 such adverse reactions occur, dosage should be reduced or therapy be interrupted and appropriate countermeasures

Risk	What is known	Preventability
		should be taken. Methotrexate therapy should only be resumed with caution, under close assessment of the necessity for treatment and with increased alertness for possible reoccurrence of toxicity.
Liver impairment/liver toxicity	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. If bilirubin is > 5 mg/dl (85.5 µmol/l), methotrexate is contraindicated. 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	As methotrexate is eliminated mainly through kidneys,	Methotrexate should be used with caution in patients with

Risk	What is known	Preventability
	increased methotrexate concentrations in serum are to be expected in case of kidney insufficiency, which may result in severe undesirable effects.	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. 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 infections caused by the cytomegalo virus are listed as possible methotrexate adverse drug reactions. Individual cases of lymphoma, which abated in a number of cases once methotrexate treatment had been discontinued, are also listed as adverse drug reaction. However, in a recent study, it was not possible to establish that methotrexate therapy increases the incidence of lymphomas.	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. Therapy must be discontinued if malignant lymphomas occur.

Risk	What is known	Preventability
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.	Methotrexate must not be used, if the patient has ulcers(sores) of the oral cavity and known active stomach-intestinal ulcer disease. During therapy (at least once a month during the first six months and every three months thereafter) examination of the mouth and throat for mucosal changes should be performed.
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), 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.	Before beginning methotrexate therapy or re-instituting methotrexate therapy after a rest period chest x-ray should be taken. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent, dry, irritating cough, general illness, shortness of breath, chest pain, fever. Methotrexate should be withdrawn from patients with pulmonary symptoms and a thorough investigation (including chest x-ray) 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	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

Risk	What is known	Preventability
	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).	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 (at least once a month during the first six months and every three months thereafter), complete blood count with differential blood count and platelets should be taken. Patients simultaneously taking blood toxic medicinal products (e.g. leflunomide) should be monitored closely with blood count and platelets.
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; it has been reported to cause foetal death and/or congenital abnormalities. Exposure of a limited number of pregnant women (42) resulted in an increased incidence (1:14) of malformations (cranial, cardiovascular and extremital). If methotrexate is discontinued prior to conception, normal pregnancies have been reported. Methotrexate passes into breast milk and may cause toxicity in nursing infants.	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, 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

Risk	What is known	Preventability
		and at least 6 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 amount of sperm (oligospermia), menstrual dysfunction, and absence of menstruation (amenorrhoea) in humans, during and for a short period after cessation of therapy. In addition, methotrexate causes embryotoxicity, abortion and foetal defects in humans. Therefore, the possible risks of effects on reproduction should be discussed with patients of childbearing potential. As methotrexate can be genotoxic, all women who wish to become pregnant are advised to consult a genetic councelling centre, if possible, already prior to therapy, and men should seek advice about the possibility of sperm preservation before starting therapy.
Accidental exposure/contact with skin	Any contact of methotrexate with skin and mucosa is to be avoided. In case of contamination, the affected parts are to be rinsed immediately with plenty of water. Pregnant health care professionals should not handle and/or administer methotrexate.
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 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 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.

The Summary of Product Characteristics and the Package leaflet for this product can be found in the national authority's web page.

This medicine has no additional risk minimisation measures.