8.2 Part VI - II.2 Elements for a Public Summary

8.2.1 Part VI - II.2.1 Overview of disease epidemiology

Acute lymphoblastic leukemia (ALL) is the most common type of cancer and leukaemia in children in the United States. ALL accounts for 26% of all cancers in children up to 14 years of age, and for 75% of pediatric leukemia cases.

In adults, this disease is less common than acute myelogenous leukaemia (AML). Approximately 1000 new cases of ALL occur in adults each year. However, due to the fact that there are more adults than children, the number of cases seen in adults is comparable to that seen in children. ALL is slightly more common in males than in females.

Worldwide, the most new cases of ALL occur in Italy, the United States, Switzerland, and Costa Rica. (Seiter K 2014)

Breast cancer is by far the most frequent cancer among women with an estimated 1.38 million new cancer cases diagnosed in 2008 (23% of all cancers), and ranks second overall (10.9% of all cancers). It is the most common cancer both in developed and developing regions with around 690,000 new cases estimated in each region. New diagnosed cases vary from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe, and are high (> 80/100,000 women) in developed regions of the world (except Japan) and low (less than 40/100,000 women) in most of the developing regions.

The range of mortality rates is much less (approximately 6-19/100,000) because of the more favourable survival of breast cancer in developed regions. As a result, breast cancer ranks as the fifth cause of death from cancer overall, but it is still the most frequent cause of cancer death in women in both developing and developed regions, where the estimated number of deaths is almost equal to the estimated number of deaths from lung cancer. (Ferlay et al., 2010)

In the United States, 400 new cases of **osteosarcoma** occur per year (4.8 per million people < 20 y). 63% (59% for males, 70% for females) of patients diagnosed between 1974 and 1994 survived 5 years.

Slightly more blacks than whites are affected:

- Blacks: 5.2 cases per million people per year (persons < 20 years)
- Whites: 4.6 cases per million people per year

Slightly more males than females are affected. In males, it is 5.2 per million per year. In females, the incidence is 4.5 per million per year.

Osteosarcoma is very rare in young children (0.5 cases per million people per year in children < 5 years). However, the number of patients affected from osteosarcoma increases steadily with age, increasing more dramatically in adolescence, corresponding with the adolescent growth spurt.

- Age 5-9 years: 2.6 (black) or 2.1 (white) cases per million people per year
- Age 10-14 years: 8.3 (black) or 7 (white) cases per million people per year
- Age 15-19 years: 8.9 (black) or 8.2 (white) cases per million people per year (Mehlman CT – Osteosarcoma Overview - 2012)

8.2.2 Part VI - II.2.2 Summary of treatment benefits

Methotrexate is a well-established drug which therapeutic effect and safety is already well known and is evident from the available scientific literature. Methotrexate interferes with the growth of certain cells in the body that reproduce quickly (anti-tumour agent), it reduces undesired reactions of the body's own defence mechanism (immunosuppressant), and it has anti-inflammatory effects. Among the disease modifying antirheumatic drugs, Methotrexate has a leading position due to its efficacy and

relatively good tolerability. It is a gold standard for the testing and validation of new treatment options in this field.

Acute lymphoblastic leukaemia (ALL)

Chemotherapy is standard treatment of ALL. Patients are evaluated for entry into well-designed clinical trials. If a clinical trial is not available, the patient can be treated with standard therapy. The most important cytostatics used in therapy protocols are vincristine, daunorubicin, doxorubicine, asparaginase, methotrexate, cyclophosphamide, cytarabine, mercaptopurine, prednisone and dexamethasone.

Stem cell transplantation is conducted in patients with a high risk of ALL relapse. Furthermore, supportive care with blood products, infection prophylaxis and therapy, and pain treatment are applied. (AWMF 2008)

Breast cancer

Breast cancer is usually treated with surgery, which may be followed by chemotherapy or radiation therapy, or both. One of the most common chemotherapy regimens combines cyclophosphamide with doxorubicin ("AC"). A taxane drug, such as docetaxel, can be added ("CAT"). Another common treatment is cyclophosphamide, methotrexate, and fluorouracil ("CMF"). (ACS – Chemotherapy for breast cancer - 2014) Hormone receptor-positive cancers (oestrogen- and progesterone- receptors) are often treated with hormone-blocking therapy, e.g. tamoxifen, anastrozole, letrozole. Monoclonal antibodies like trastuzumab (antibody to HER2, a cell receptor that is especially active in some breast cancer cells; only effective in case of HER2 overexpression of the cancer), or other immune-modulating treatments, may be administered in certain cases of metastatic and other advanced stages of breast cancer. (ACS – Hormone therapy for breast cancer - 2014)

Osteosarcoma

Osteosarcomas are surgically treated. Due to the high risk of micrometastases, the use of postoperative chemotherapy is critical for the treatment of patients with osteosarcoma. Preoperative chemotherapy facilitates subsequent surgical removal by causing tumor shrinkage but also provide patients in whom there has been a good response to this chemotherapy (>95% tumor cell kill) a better prognosis than those whose tumors do not respond as favorably. (Mehlman CT – Osteosarcoma Treatment & Management - 2012) The so far best published results were achieved with polychemotherapy protocols, which contain several of the following cytostatics: adriamycine, high-dose methotrexate with folate, cisplatin and ifosfamide. Also the immune modulating liposomal muramyl-tripeptid-phosphatidyl-ethanolamine in combination with chemotherapy in case of completely resected, localised osteosarcomas in patients <30 years is approved.

In individual cases, radiation therapy is applied. (AWMF 2010)

8.2.3 Part VI - II.2.3 Unknowns relating to treatment benefits

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

8.2.4 Part VI - II.2.4 Summary of safety concerns

Table 8-11 Important identified risks

Risk	What is known	Preventability
Increased risk of tumours (Increased risk of neoplasia)	Malignant lymphomas, a type of cancer of the immune system cells called lymphocytes, may occur in patients receiving low-dose Methotrexate.	If malignant lymphomas occur Methotrexate must be discontinued. If lymphomas should fail to regress spontaneously, initiation of malicious cell killing therapy is

Risk	What is known	Preventability
		required.
Deformities in the unborn child (including death of the unborn and abortion) (Teratogenicity (including foetal death and abortion))	Methotrexate can cause birth defects, harm unborn babies or cause miscarriages.	During treatment with Methotrexate, strict contraception is absolutely essential. This requirement applies to both men and women. In women of childbearing age, pregnancy must be excluded prior to beginning treatment. Women of childbearing age must use reliable contraception for at least 4 weeks prior to starting treatment, and medical advice on appropriate methods of contraception should be sought if necessary. Men using Methotrexate should use condoms when having sexual intercourse with a partner of child bearing age. After discontinuation of Methotrexate, patients should wait for at least 6 months before considering having children.
Risk of contamination	Contamination with Methotrexate during administration or during disposal can lead to severe side effects.	Methotrexate must not be discarded into waste water. Used Methotrexate pre-filled syringes should be discarded in appropriate sharp bins. Skin and mucosal contacts with methotrexate are to be avoided. In the case of contamination, the parts concerned should be rinsed with plenty of water. Pregnant carers or pregnant relatives should not be involved in the administration of Methotrexate pre-filled syringes as unintentional contact with methotrexate (e. g. through a needle injury) might cause deformities in the unborn child.
Toxic effects on the liver (Hepatotoxicity)	Methotrexate can have a toxic effect on the liver.	Treatment should not be initiated or should be discontinued if there are any abnormalities in liver function tests or liver tissue examinations, or if these develop during therapy. Such abnormalities should return to normal within two weeks; after

Risk	What is known	Preventability
		which, treatment may be resumed at the discretion of the doctor. Additional medications that are toxic for the liver should not be given during treatment with methotrexate unless clearly necessary and alcohol consumption should be avoided or greatly reduced.
Toxic effects on the lung (Pulmonary toxicity)	Severe inflammation of lung tissue (pneumonitis) may occur and deaths have been reported. Symptoms typically include breathlessness, cough (especially a dry non- productive cough), chest pain and fever.	Patients should be monitored at each follow-up visit for lung symptoms. Methotrexate should be withdrawn from patients with lung symptoms and a thorough investigation (including chest x-ray) should be made to (exclude infection and tumors. If methotrexate induced lung disease is suspected treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.
Toxic effects on the blood cells (Haematological toxicity)	Blood count changes induced by Methotrexate may occur abruptly and at apparently safe doses.	In the event of any significant drop in white blood cells or platelets, treatment must be discontinued immediately and appropriate supportive therapy instituted. Patients must be instructed to report all signs and symptoms suggestive of infection. In patients concomitantly taking medications that are toxic for the blood (e.g. leflunomide), the blood count and platelets should be closely monitored. Administration of additional medicinal products that are toxic for the blood (e.g. metamizole) increases the probability of severe toxic effects of methotrexate for the blood. During longer-term therapy with methotrexate bone marrow biopsies are to be performed.
Toxic effects on the digestive tract (Gastrointestinal toxicity)	Very commonly (more than 1 user in 10) inflammation and ulcers in the mouth and throat, loss of appetite, nausea (feeling sick) and vomiting are observed under therapy with methotrexate,	Even when methotrexate is used at low doses, serious side effects can occur. In order to recognise these in good time, the treating physician must carry out check-ups.

Risk	What is known	Preventability
	commonly (1 to 10 users in 100) diarrhoea, uncommonly (1 to 10 users in 1,000) ulcers and bleeding in the digestive tract, rarely (1 to 10 users in 10,000) inflammation of the digestive tract, black or tarry stools, inflamed gums, abnormal digestion, and very rarely (less than 1 user in 10,000) vomiting blood and severe complication of the digestive tract.	Appointments should not be missed.
Infection / disorders of the immune system (Infection / immunological toxicity)	Uncommonly (1 to 10 users in 1,000) shingles occurred under methotrexate therapy, very rarely (less than 1 user in 10,000) infections, inflammation of the protective membranes covering the brain and spinal cord, so called meningitis, whole-body inflammation caused by an infection, so called sepsis, fever, bacterial and fungal infections of the lung, disorders of the immune system, infection around a fingernail, fungal infections. Very rarely (less than 1 user in 10,000) reactivation of chronic hepatitis is observed under therapy with methotrexate.	Methotrexate must not be used if a patient has a severe or existing infection such as tuberculosis and HIV). Special care should be taken if a patient has inactive, prolonged infections (e.g. tuberculosis, hepatitis B or C, shingles (herpes zoster)). Live vaccines should not be given during treatment with methotrexate. Even when methotrexate is used at low doses, serious side effects can occur. In order to recognise these in good time, the treating physician must carry out check-ups and laboratory tests. Before treatment is started the doctor may carry out blood tests. Also chest X-ray may be conducted. Further tests may also be done during and after treatment. Appointments for blood tests should not be missed. If the results of any of these tests are abnormal, treatment will only be resumed when all readings are back to normal.
Toxic effects on the kidneys (Renal toxicity)	Rarely (1 to 10 users in 10,000) kidney failure, little or no urine produced, and/or frequent urination were observed under treatment with methotrexate and very rarely (less than 1 user in 10,000) protein in the urine (can be detected by a test carried out by a doctor).	Methotrexate must not be used if a patient has a significant kidney disease. Special care should be taken if a patient has/had any kidney disease, Among others, the treatment dose of methotrexate will depend on how well the patient's kidneys are working. If the patient has problems with the kidneys the doctor may reduce the dose depending on how the kidneys

Risk	What is known	Preventability
		work. Even when methotrexate is used at low doses, serious side effects can occur. In order to recognise these in good time, the treating physician must carry out check-ups and laboratory tests. If a patient has or had any kidney disease, special care should be taken with methotrexate pre-filled syringes. If a patient has significant kidney disease (the doctor decides the severity of the disease), methotrexate pre-filled syringes should not be used. Before treatment is started the doctor may carry out blood tests, and also check how well the kidneys are working. Further tests may also be done during and after treatment. Appointments for blood tests should not be missed. If the results of any of these tests are abnormal, treatment will only be resumed when all readings are back to normal. The dose of this medicine among others will depend on how well the patient's kidneys are working.
Skin toxicity	The skin can be extremely sensitive to sunlight or other forms of light during the treatment with methotrexate. Severe peeling or blistering of the skin and tiny red spots on the skin were observed under treatment with methotrexate. Commonly (1 to 10 users in 100) occurred measle-like rash (alone), redness and itching, uncommonly (1 to 10 users in 1,000) nettle rash (alone), light sensitivity, brown skin, severe peeling or blistering of the skin, hair loss, painful lesions of scaly patches caused by psoriasis and formation of clusters of vesicles that resemble the skin lesions of	Sunlight and solarium should be avoided. Even when methotrexate is used at low doses, serious side effects can occur. In order to recognise these in good time, the treating physician must carry out check-ups. Appointments should not be missed.

Risk	What is known	Preventability
	herpesvirus infection, rarely (1 to 10 users in 10,000) acne, red or purple spots, bruise, and inflammation of the skin and very rarely (less than 1 user in 10,000) boils, small blood vessels in the skin, damage to the blood vessels of the skin, lumps in the armpit or groin and slow wound healing. Methotrexate is not blister forming and should therefore not cause damage to skin. If the compound should get in contact with the skin, the skin should still be rinsed immediately with water, however. Transient stinging can be treated with a mild cream.	
Interaction with drugs which reduce gastric acid production, antibiotics and drugs causing low level of folate / vitamin B9 in the body and with other cancer treatments (Drug-drug interaction with proton pump inhibitors, antibiotics and drugs causing folate deficiency, and with other cytostatics)	Concomitant administration of proton-pump inhibitors like omeprazole or pantoprazole and methotrexate can lead to interactions. The excretion of methotrexate and/or a degradation product by the kidneys could be reduced. Some antibiotics (so called penicillines, glycopeptides, sulfonamides, ciprofloxacin and cefalotin) can disturb the degradation of methotrexate so that toxicity on blood cells and digestive system may occur. If medications which cause a low level of folate in the body (e.g. sulphonamides, trimethoprim-sulphamethoxazole) and methotrexate are used in parallel, this can lead to increased methotrexate toxicity. Methotrexate in treatment for malignant diseases is normally used in combination with other cytostatics. Additive toxicity can be expected during combination chemotherapy with medicines with the same pharmacological effect, especially regarding toxicity on the bone marrow, kidneys, digestive	The doctor or pharmacist should be informed if the patient is taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal or natural medicinal products. Also if the patient is prescribed another medicine while the methotrexate treatment is still ongoing, the doctor should be informed. People receiving chemotherapy for a cancer with a high cell turnover rate, especially lymphomas and leukaemias, should receive prophylactic allopurinol (a drug which inhibits uric acid production) as well as fluid infusion to maintain high urine output (> 2.5 l/day). Rasburicase (drug which degrades uric acid) can be used as alternative to allopurinol for people who are high-risk in developing tumour lysis syndrome. Even when methotrexate is used at low doses, serious side effects can occur. In order to recognise these in good time, the treating physician must carry out check-

Risk	What is known	Preventability
	tract and lungs.	ups. Appointments should not be missed.
Toxic effects on the nervous system (Neurological toxicity)	Side effects affecting the central nervous system, such as tiredness and dizziness, may occur during treatment with methotrexate. In some cases, the ability to drive vehicles and/or use machines may therefore be impaired. If a patient feels tired or dizzy, he/she should not drive or use machines. Commonly (1 to 10 users in 100), headache, tiredness, sleepiness were observed under treatment with methotrexate, uncommonly (1 to 10 users in 1,000) spinning sensation, confusion, depression, fits (convulsions), rarely (1 to 10 users in 10,000) mood alterations, very rarely (less than 1 user in 10,000) meningitis, pins and needles, changes in sense of taste (metallic taste), loss of consciousness, inflammation of the lining of the brain causing paralysis or vomiting.	Even when methotrexate is used at low doses, serious side effects can occur. In order to recognise these in good time, the treating physician must carry out check-ups. Appointments should not be missed.
Impaired male and female fertility	Methotrexate may be genotoxic. This means that the medicine may cause genetic mutation. Methotrexate can affect sperm and egg production. Since treatment with methotrexate may lead to infertility, it might be advisable for male patients to look into the possibility of sperm preservation before starting treatment. Very rarely (less than 1 user in 10,000) low sperm production, abnormal periods, and infertility were observed under treatment with methotrexate.	Even when methotrexate is used at low doses, serious side effects can occur. In order to recognise these in good time, the treating physician must carry out check-ups. Appointments should not be missed.
Tumour lysis syndrome	The tumour lysis syndrome is a group of metabolic complications that can occur after treatment of cancer, usually lymphomas and leukaemias, and sometimes even without treatment. These complications are caused by the	People receiving chemotherapy for a cancer with a high cell turnover rate, especially lymphomas and leukaemias, should receive prophylactic allopurinol (a drug which inhibits uric acid production) as well as

Risk	What is known	Preventability
	breakdown products of dying cells and include increased potassium, increased phosphates, increased uric acid in the blood and increased uric acid in the urine, decreased calcium in the blood, and consequent kidney disease and acute kidney failure. Symptoms can be heart rhythm disturbances, muscle weakness or paralysis, tetany (involuntary muscle contractions), sudden mental incapacity, including emotional lability, parkinsonian movement disorders, muscular disease, lactic acidosis (low pH in body tissues and blood with lactic acid buildup)	fluid infusion to maintain high urine output (> 2.5 l/day). Rasburicase (drug which degrades uric acid) can be used as alternative to allopurinol for people who are high-risk in developing tumour lysis syndrome. Even when methotrexate is used at low doses, serious side effects can occur. In order to recognise these in good time, the treating physician must carry out check-ups. Appointments should not be missed.
Cell death in soft tissue and bones associated with concomitant radiation therapy (Soft tissue necrosis and osteonecrosis associated with concomitant radiation therapy)	Radiotherapy during use of methotrexate can increase the risk of cell death in soft tissue and bones.	Even when methotrexate is used at low doses, serious side effects can occur. In order to recognise these in good time, the treating physician must carry out check-ups. Appointments should not be missed.

Table 8-12 Important potential risks

None

Table 8-13 Missing information

Risk	What is known
Use in children younger than 3 years	Use in children < 3 years of age is not recommended due to the insufficient experience in this age group.

8.2.5 Part VI - II.2.5 Summary of additional risk minimization 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 special conditions and restrictions for its safe and effective use (additional risk minimisation measures). How they are implemented in each country will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimization measures are for the following risks:

Deformities in the unborn child (including death of the unborn and abortion)

Risk minimization measure(s): Information Brochure for patients, relatives and medical personnel

Objective and rationale: Patients and HCPs to understand the risk of teratogenicity and the appropriate management of this risk to minimise its occurrence and to ensure the safe and effective use of Methotrexate.

Summary description of main additional risk minimisation measures:

Extended information brochure for patients emphasizing the need of contraception in child-bearing age.

Methotrexate causes embryotoxicity, abortion and foetal defects in humans.

In patients of childbearing age (men and women) a strict contraception is absolutely essential as Methotrexate is teratogenic. A possible pregnancy has to be reported to the treating physician.

Pregnant HCP or carers, e.g. relatives should not be involved in the administration of Methotrexate injectable products as unintentional contact with methotrexate (e. g. through a needle injury) might cause deformities in the unborn child.

Contamination

Risk minimization measure(s): Information Brochure for patients, relatives and medical personnel

Objective and rationale: Patients, relatives and HCPs to understand the risk of contamination during administration or disposal and the appropriate management of this risk to minimise its occurrence and to ensure the safe and effective use of Methotrexate.

Summary description of main additional risk minimisation measures: Extended information brochure for patients, relatives and medical personnel with mention of correct handling and disposal (e.g. safe recapping, disposal as special waste either via local pharmacy or in the context of a special waste collection).

Information brochure for patients, relatives and medical personnel will be provided emphasizing the need of contraception in child-bearing age and detailing correct handling and disposal (e.g. safe recapping, disposal as special waste either via local pharmacy or in the context of a special waste collection).

There is risk of accidental exposure to those administering the product, and risk of contamination on disposal.

Used Methotrexate pre-filled syringes should be discarded in appropriate sharp bins to avoid a possible contamination of other people in the household (e.g. due to needle injury) and of the environment. Sharp bins are available on prescription. Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

8.2.6 Part VI - II.2.6 Planned post authorization development plan

None

8.2.7 Part VI - II.2.7 Summary of changes to the Risk Management Plan over time

Table 8-14 Major Changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Ebetrexat 20 mg/ml solution for injection and Ebetrexat 10 mg/ml solution for injection, pre-filled syringe (Methotrexat)	May 2009		
Methotrexate “Ebewe” 10 mg/ml solution for injection	Not provided		
Methotrexat «Ebewe» 10 mg/ml solution for injection, Ebetrexat 10 mg/ml solution for injection, pre-filled syringe (Methotrexat)	14 Apr 2011		
Methotrexate 10 mg/ml, 20 mg/ml Solution for injection pre-filled syringe RMP version 2.0	15 Apr 2013	No changes to risks and commitments	The three existing RMPs for Methotrexate for different procedures were merged to one single RMP (a risk management plan is in place for Ebetrexat 20 mg/ml solution for injection and Ebetrexat 10 mg/ml solution for injection, pre-filled syringe (Methotrexat), dated May 2009; a second risk management plan is in place for Methotrexate “Ebewe” 10 mg/ml solution for injection; a third risk management plan is in place for Methotrexat «Ebewe» 10 mg/ml solution for injection, Ebetrexat 10 mg/ml solution for injection, pre-filled syringe (Methotrexat), dated Apr 2011 approved in the procedures AT/H/0192/001 and AT/H/0222/001). No additional risks were included. This combined version of the RMP was updated to the new RMP template for generic products according to Guideline on good pharmacovigilance practices (GVP) Module V- Risk Management Systems.
Methotrexate pre-filled	23 Jul 2014	No changes to risks	Internal update (RMP not

Version	Date	Safety Concerns	Comment
syringes RMP version 3.0		and commitments	submitted): - Further strengths (7.5 mg/ml, 25 mg/ ml) were included on the first page, in section 1.2. and Annex 3 - Educational material was updated to include the new text and images on the needle safety guard.
Methotrexate 10 mg/ml, 20 mg/ml solution for injection pre-filled syringes. RMP-Version 3.1	13 Nov 2014	Gastrointestinal toxicity, Infection / immunological toxicity, Renal toxicity, Skin toxicity, Reactivation of hepatitis B and C, Drug-drug interaction with proton pump inhibitors, Drug-drug interaction with other cytostatics (in cancer treatment), Neurological toxicity, Tumour lysis syndrome (in cancer treatment), Soft tissue necrosis and osteonecrosis associated to concomitant radiation therapy (in cancer treatment), Impairment of fertility including oligospermia and menstrual disorders	Following the requirements of the RMS in its DAY 40 ASSESSMENT REPORT regarding the RMP for Methotrexat ”Ebewe” Solution for injection pre-filled syringe, 10mg/ml (Methotrexate): - these risks were included as additional important identified risks in the RMP with respective filling of all relevant chapters.
		Potential for overdose	- this already present important potential risk was updated to “Potential for overdose in the elderly if daily doses are accidentally given instead of weekly doses in rheumatoid arthritis (applicable for Methotrexate used for rheumotologic diseases)”
		Teratogenicity	- this already present important identified risk was updated to Teratogenicity (including foetal death and abortion)
		Teratogenicity (including foetal death and abortion) and Risk of contamination	- Part V.3. “Summary table of risk minimization measures”, Table 8-1 “Risk minimization measures by safety concern”, Table 6-2 “Summary table of Risk Minimization Measures” and Part VI.2.5 “Summary of additional risk

Version	Date	Safety Concerns	Comment
			minimization measures by safety concern", the details on the educational material related to these risks were more updated to describe it more precisely.
		None	- in "Product details" for each product, the indication and posology for Methotrexate 10 mg/ml solution for injection PFS and 20 mg/ml solution for injection PFS and the respective earliest approval and launch data were updated. - in Table 8-2 "Risk minimization measures by safety concern", the respective citations regarding important identified and potential risks from the SmPCs were included. - the relevant SmPCs were included in Annex 2. - Part VI.2 "Elements for a Public Summary" was updated to the format of the currently valid EU-RMP template and information related to the indications of malignant diseases included. Additionally, the amendments of RMP version 3.0 concerning the 7.5 mg/ml and 25 mg/ ml pre-filled syringes on the first page and in section 1.2. and the educational material (new text and images on the needle safety guard) were included.
Methotrexate solution for injection pre-filled syringes. RMP-Version 3.2	20 Apr 2015		Following the RMS' FINAL ASSESSMENT REPORT ON PSUR concerning MTX Sandoz 20 mg/ml solution for injection in pre-filled syringes dated 17 Feb 2015, the following was implemented in the RMP:
		Important identified risk "Increased risk of neoplasia (lymphoma)"	changed to "Increased risk of neoplasia"
		Important identified risks "Safety in patients with renal impairment", "Interactions with	added as new risks

Version	Date	Safety Concerns	Comment
		antibiotics and drugs causing folate deficiency"	
		Important potential risk "Potential for overdose in the elderly if daily doses are accidentally given instead of weekly doses in rheumatoid arthritis (applicable for Methotrexate used for rheumotologic diseases)"	changed to important identified risk
		Missing information "Use in children younger than 3 years"	added as new missing information. Also added in Part VI.2.3 Unknowns relating to treatment benefits.
		All risks	grouped in categories - for treatment of cancer and rheumatologic diseases, - for treatment of rheumatologic diseases and - for treatment of cancer.
Methotrexate solution for injection pre-filled syringes. RMP-Version 3.3	23 Jun 2015		Updates according to the Day 20 assessment report of BfARM:
		Renal toxicity and safety in patients with renal impairment	merged under the risk of renal toxicity and risk minimization measures were provided a) in general and b) for patients with renal impairment in one section.
		Drug interactions with proton-pump inhibitors, antibiotics and drugs causing folate deficiency	summarized in one section.
		Reactivation of hepatitis B and C	described under infection/immunological toxicity.
		Impairment of fertility including oligospermia and menstrual disorders	shortened to impaired male and female fertility.
		Overdose due to medication errors	updated with a short explanation.
			Separate Parts VI for the

Version	Date	Safety Concerns	Comment
			rheumatological (VI-I) and cancer (VI-II) indications were included