III.1. Elements for a Public Summary

III.1.1. Overview of disease epidemiology

Highly active relapsing (occurring in isolated attacks) multiple sclerosis associated with rapidly evolving disability

Multiple sclerosis (MS) is a global disease affecting the insulating covers of the nerve cells in the brain and spinal cord. Thirty of 100,000 people suffer from multiple sclerosis globally. Multiple sclerosis occurs more often in Europe, followed by the Eastern Mediterranean, the Americas, the Western Pacific, South-East Asian and African regions. The symptoms usually manifest between the age of 25 and 32 years. The disease is two times more common in women than in men (WHO, 2008). The cause of MS is unknown, genetic and environmental factors are believed to play a role.

Advanced stage (metastatic form) of breast cancer

Breast cancer is the most common cancer in women and comprises 18% of all female cancers (McPherson et al., 2000). Approximately 7% of women with breast cancer are diagnosed before the age of 40 years (Anders et al., 2009). The risk of breast cancer in women who have their first child after the age of 30 is about twice that of women who have their first child before the age of 20 (McPherson et al., 2000). Women who start menstruating early in life or who have a late menopause have an increased risk of developing breast cancer (McPherson et al., 2000). Both oral contraceptives (medications: prevent pregnancy) and hormonal therapy for menopause cause a small increase in breast-cancer risk (Key et al., 2001). There are also some risk factors related to lifestyle or environment.

Non-Hodgkin's lymphoma (NHL), a form of lymph node cancer

According to the data of the WHO International Agency for Research on Cancer (IARC), 16 of 100,000 people are affected by NHL globally. In Europe, 40 of 100,000 suffer from NHL (IARC, 2012, 03.02.2017). Non-Hodgkin's lymphomas are more common in men than in women (Grulich and Vajdic, 2005). Non-Hodgkin's lymphoma is the 6th most commonly diagnosed cancer in US males and the 5th in US females (Alexander et al., 2007). Occurrence rates increase with age for both male and female. Globally, the disease rates are highest in North America and Australia (Alexander et al., 2007). The cause of NHL is not finally understood.

Acute myeloid leukaemia (AML) in adults, a cancer of the blood in which the bone marrow makes too many white blood cells

The rate of occurrence of AML in European adults is 5-8 cases per 100,000 (Fey and Dreyling, 2009). Acute myeloid leukaemia is characterised by rapid growth of abnormal white blood cells that accumulate in the bone marrow (tissue in the interior of bones) and interfere with the production of normal blood cells. AML is the most common form of acute leukaemia among adults and accounts for the largest number of annual deaths due to leukaemia in the United States (O'Donnell et al., 2012). The disease occurs more frequently in older people.

Blast crisis (terminal phase) in chronic myeloid leukaemia (CML), i.e. a cancer of the white blood cells at a stage where it is difficult to control the number of white blood cells

Chronic myeloid leukaemia can be subdivided into three phases. In the first stage, the disease develops gradually and progresses slowly. This phase is followed by the accelerated phase resulting in the third phase 'blast crisis'. The terminal phase of the chronic myeloid leukaemia ('blast crisis') is comparable to the acute myeloid leukaemia, the number of white blood cells is difficult to control.

Occurrence rate of chronic myeloid leukaemia increases with age (Chen et al., 2013). Exposure to radiation appears to be a risk factor.

Palliation (e.g. pain relief) related to advanced castrate resistant prostate cancer

In 2012, prostate cancer was the most common cancer in men in Europe, with 489 cases in 100,000 men. Prostaste cancers accounted for 22% of all new cases of cancer in men (IARC, 2012, 03.02.2017). The occurrence of prostate cancer is strongly related to age, with the highest occurrence rates being in older men (Cancer Research UK, 2016b). Beside age, obesity and family history appear to be risk factors.

III.1.2. Summary of treatment benefits

Highly active relapsing (occurring in isolated attacks) multiple sclerosis associated with rapidly evolving disability (impairment)

Interferon-beta is used for the treatment of multiple sclerosis as first-line therapy (primary therapy). Mitoxantrone is used as second line therapy (secondary therapy) in multiple sclerosis for patients who failed other therapy or do not tolerate it.

Advanced stage (metastatic form) of breast cancer

Definitive cure is not achievable currently and benefit from treatment is alleviation of symptoms without a cure. The primary therapy is often tamoxifen for some kind of advanced breast cancer. Mitoxantrone may be used as a single agent or in combination with other medication (Heidemann et al., 2002).

Non-Hodgkin's lymphoma (NHL), a form of lymph node cancer

Chemotherapy is the most common treatment option for NHL, typically with CHOP or R-CHOP (chemotherapy combination used in the treatment of NHL) for aggressive lymph node cancer. Irradiation of lymph nodes is sometimes used after chemotherapy whereas transplantation of stem cells is infrequently used for patients with recurrent cancer. Mitoxantrone is a therapeutic alternative to doxorubicin (another medication used to treat cancer) (Armitage, 2002).

Acute myeloid leukaemia (AML) in adults, a cancer of the blood in which the bone marrow makes too many white blood cells

Chemotherapy is given as first treatment in AML, which is in some patients followed by consolidation therapy (that is given after cancer has disappeared following the initial therapy). For patients who become ill again after apparent recovery, the only proven therapy which may cure the cancer is transplantation of stem cells. Mitoxantrone has shown to be effective in the treatment of AML (Arlin et al., 1990).

Blast crisis (terminal phase) in chronic myeloid leukaemia (CML), i.e. a cancer of the white blood cells at a stage where it is difficult to control the number of white blood cells

Once CML progressed to blast crisis second generation medications (dasatinib and nilotinib) should be tried. If return to CML or a complete disappearing of symptoms is achieved, transplantation of stem cells is recommended. If second generation medications fail, conventional chemotherapy in various combinations including mitoxantrone remain an option.

Palliation (e.g. pain relief) related to advanced castrate resistant prostate cancer

There is no cure for castrate resistant prostate cancer (CRPC). Docetaxel in combination with prednisone (corticosteroid) is the standard chemotherapy in CRPC. Mitoxantrone in combination with corticosteroids given improves pain control and quality of life in patients with advanced CRPC.

Mitoxantrone hydrochloride has been used for over 30 years. Its risks and benefits have been established for a long time with a positive benefit-risk balance.

III.1.3. Unknowns relating to treatment benefits

The efficacy of mitoxantrone has been demonstrated in the approved indications by various clinical trials as well as by the use in clinical practice over years.
No studies were performed concerning use of mitoxantrone in patients with kidney or liver impairment. Therefore, mitoxantrone should be used with caution in these patients. For patients with liver impairment dose adjustment may be necessary. However, there are insufficient data that allows for dose adjustment recommendations. There does not seem to be relevant differences in pharmacokinetics (the action of medications in the body over a period of time) of mitoxantrone between elderly and young adult patients. The effect of gender, race, renal impairment and hepatic impairment on mitoxantrone pharmacokinetics is unknown.

III.1.4. Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Damage to the function of the heart, severe condition where the heart cannot anymore pump enough blood (Risk on cardiotoxicity: Cardiac function/myocardial toxicity)	Mitoxantrone may damage the heart and cause a deterioration of the heart function or in more severe cases heart failure. Patients are more prone to these side effects if they take higher doses of mitoxantrone or if the heart is not working well, if they had prior treatment of the chest with radiation, if they already use other medicines that affect the heart, or if they had previous therapies with a group of chemotherapeutic agents called anthracyclines or anthracenediones, such as daunorubicin or doxorubicin. Damage to the heart muscle may occur either during therapy with mitoxantrone hydrochloride or months to years after termination of therapy. Potential signs or symptoms of heart problems are chest pain, breathlessness, changes in the heartbeat (fast or slow), and	The individual dose of mitoxantrone is calculated by the treating physician, and the lowest possible dose to achieve the desired clinical effect should be chosen. Heart function tests should be done before start of treatment and at regular intervals during therapy. In patients receiving mitoxantrone for the treatment of multiple sclerosis heart function will be tested before the start of therapy, prior to each subsequent dose and yearly for up to 5 years after the end of therapy.

Important identified risks		
Risk	**What is known**	**Preventability**
	fluid retention (swelling) in the ankles or legs. In patients treated with **mitoxantrone for cancer** the PIL section 4 "Possible side effects" states the following: Congestive heart failure (severe condition where the heart cannot anymore pump enough blood) may affect up to 1 in 10 people. An irregular heart beat or slowed heart beat, an abnormal electrocardiogram, or a reduction of the volume of blood that the left ventricle can pump, with no symptoms, may affect up to 1 in 100 people. Damages to the heart muscle preventing it from pumping properly (cardiomyopathy) may affect up to 1 in 1,000 people. In patients treated with **mitoxantrone for multiple sclerosis** the PIL section 4 "Possible side effects" states the following: An irregular heart beat, an abnormal electrocardiogram, or reduction of the volume of blood that the left ventricle can pump, with no symptoms, may affect up to 1 in 10 people. A severe condition where the heart cannot anymore pump enough blood (congestive heart failure), damages to the heart muscle preventing it from pumping properly (cardiomyopathy), or slowed heart beat may affect up to 1 in	

Important identified risks		
Risk	**What is known**	**Preventability**
	100 people.	
Cancer of white blood cells (acute myeloid leukaemia, AML) and a bone marrow disorder that causes abnormally shaped blood cells and leads to leukaemia (myelodysplastic syndrome) (Risk on haematotoxicity: Secondary acute myeloid leukaemia and myelodysplastic syndrome)	A group of anticancer medicines (topoisomerase II inhibitors), including mitoxantrone, may cause a cancer of white blood cells (acute myeloid leukaemia, AML) or a bone marrow disorder that causes abnormally shaped blood cells and leads to leukaemia (myelodysplastic syndrome). These diseases may develop when mitoxantrone is used alone but especially when mitoxantrone is used in combination with other chemotherapy and/or radiotherapy. The PIL section 4 "Possible side effects" states that cancer of the white blood cells (acute myeloid leukemia) or bone marrow abnormality which causes the formation of abnormal blood cells which leads to leukemia (myelodysplastic syndrome) may affect up to 1 in 100 people treated with mitoxantrone for multiple sclerosis. The PIL section 4 "Possible side effects" states that cancer of the white blood cells (acute myeloid leukemia) or bone marrow abnormality which causes the formation of abnormal blood cells which leads to leukemia(myelodysplastic syndrome) may affect up to 1 in 100 people treated with mitoxantrone for cancer.	Patients should be informed about risks, symptoms and signs of acute leukaemia and myelodysplastic syndrome and prompted to seek medical attendance if any such symptoms should occur even after the five year period has passed.
Bone marrow suppression/	Mitoxantrone may affect the	Before patients start

Important identified risks		
Risk	**What is known**	**Preventability**
reduced activity of the bone marrow (Bone marrow suppression/myelosuppression)	blood cell counts by suppressing of the bone marrow (the spongy tissue inside the large bones) with insufficient production of the white and red blood cells and platelets. The reduced activity of the bone marrow may lead to a reduction in red blood cells with the potential signs of pale skin, feeling weak or sudden shortness of breath, to a reduction in white blood cells with an increased risk of fever or infections, and to a reduction of platelets with the potential signs of unusual bruising or bleeding, such as coughing up blood, blood in the vomit or urine, or black stools. Suppression of the bone marrow may be more severe and prolonged in patients with poor general condition, and if the patient has had chemotherapy or radiotherapy. Furthermore, the risk of severe bone marrow suppression increases when mitoxantrone is used in high doses. In patients treated with **mitoxantrone for cancer** the PIL section 4 "Possible side effects" states the following: A low number of red blood cells (anaemia) which can cause a feeling of tiredness and shortness of breath may affect more than 1 in 10 people. A blood transfusion may be required. A low number of special white blood cells (leukocytes or neutrophils) may affect more	mitoxantrone and during treatment, a blood test should be done to count the number of the blood cells. The doctor carries out blood tests more often, in which he in particular monitors the number of white blood cells (neutrophilic leucocytes) in the blood, if the patient has a low count of a specific type of white blood cells (neutrophils) (less than 1,500 cells/mm^3), or if a patient uses mitoxantrone in high doses (>14 mg/m^2 per day x 3 days). The individual dose of mitoxantrone is calculated by the doctor. The dosage of the medicine should be adjusted in accordance with the results of the blood tests.

Important identified risks		
Risk	**What is known**	**Preventability**
	than 1 in 10 people. Infections may affect more than 1 in 10 people. A low level of platelets which may cause bleeding or bruising may affect up to 1 in 10 people. A low number of special white blood cells (granulocytes) may affect up to 1 in 10 people. Reduced activity of the bone marrow or insufficient production of blood cells in the bone marrow (bone marrow failure) or abnormal number of white blood cells may affect up to 1 in 100 people. Infections, such as infections of the upper airways, infections of the urinary tract, blood poisoning (sepsis), infections caused by microorganisms which do not normally cause diseases with a healthy immune system (opportunistic infections), may affect up to 1 in 100 people. Bruising, heavy bleeding, or bleeding in the stomach or bowels (which may include blood in vomit and bleeding when emptying the bowels or black tarry stool) may affect up to 1 in 100 people. Lung inflammation (pneumonia) may affect up to 1 in 100 people. In patients treated with **mitoxantrone for multiple sclerosis** the PIL section 4 "Possible side effects" states	

Important identified risks		
Risk	**What is known**	**Preventability**
	the following: Infections, including infections of the upper airways and urinary tract, may affect up to 1 in 10 people. A low number of red blood cells (anaemia) which can cause a feeling of tiredness and shortness of breath may affect up to 1 in 10 people. A blood transfusion may be required. A low number of special white blood cells (granulocytes and leukocytes) may affect up to 1 in 10 people. An abnormal number of white blood cells may affect up to 1 in 10 people. Insufficient production of blood cells in the bone marrow (bone marrow failure), or reduced activity of the bone marrow may affect up to 1 in 100 people. A low level of platelets (which may cause bleeding or bruising), or a low number of special white blood cells (neutrophils) may affect up to 1 in 100 people. Lung inflammation (pneumonia), blood poisoning (sepsis), or infections caused by microorganisms which do not normally cause diseases with a healthy immune system (opportunistic infections) may affect up to 1 in 100 people. Unusual bruising, heavy bleeding, or bleeding in the stomach or bowels (which may include blood in vomit,	

Important identified risks		
Risk	**What is known**	**Preventability**
	bleeding when emptying the bowels or black terry stool) may affect up to 1 in 100 people. Fever may affect up to 1 in 100 people.	
Risk to the foetus and fertility (Teratogenicity/reproductive toxicity)	Mitoxantrone may cause damage to the unborn child. Therefore patients should avoid becoming pregnant. Mitoxantrone might increase the risk for transient or persistent absence of menstruation (amenorrhoea) in women of childbearing age. In men, no data are available. However, in male animals, damage to the testes and decreased sperm counts were observed. The PIL section 4 "Possible side effects" states the following: An abnormal absence of menstruation (amenorrhea) may affect up to 1 in 100 people treated with mitoxantrone for cancer. An abnormal absence of menstruation (amenorrhea) may affect more than 1 in 10 people treated with mitoxantrone for multiple sclerosis.	Mitoxantrone must not be used during pregnancy for treatment of multiple sclerosis (specifically in the first three months of the pregnancy). If a patient becomes pregnant during the treatment with Mitoxantrone, the patient must tell her doctor immediately and stop treatment with Mitoxantrone. Patients should avoid becoming pregnant. Men must use an effective method of contraception during the treatment and for at least 6 months after discontinuing the treatment. Women of child-bearing potential should have a negative pregnancy test prior to each dose and must practise effective contraception for at least 4 months after stopping the treatment with Mitoxantrone. Due to the increased risk of transitory or persistent abnormal absence of menstruation (amenorrhoea) patients should talk to their doctor if they are planning to become pregnant in the future; their eggs may need to be frozen.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**

None	N/A

Missing information	
Risk	**What is known**
Safety in patients with kidney impairment (Safety in patients with renal impairment)	The safety of mitoxantrone in patients with kidney impairment is not established. Mitoxantrone should be used with caution. Elderly patient should receive doses at the low end of the dosing range.
Safety in patients with liver impairment (Safety in patients with hepatic impairment)	The safety of mitoxantrone in patients with liver impairment is not established. For patients with liver impairment dose adjustment may be necessary as mitoxantrone clearance is reduced by liver impairment. There are insufficient data that allows for dose adjustment recommendations. Laboratory measurement cannot predict clearance of the active substance and dose adjustments. Elderly patient should receive doses at the low end of the dosing range.

III.1.5. Summary of risk minimisation measures by safety concern

Routine risk minimisation measures like Summary of Product Characteristics (SmPC) or Package Information Leaflet (PIL) are applied for all safety concerns. Furthermore, mitoxantrone has special conditions and restrictions for its safe and effective use.

Therefore, additional risk minimisation measures are intended to handle the following risks:

Important identified risks: • **Damage to the function of the heart, severe condition where the heart cannot anymore pump enough blood (Risk on cardiotoxicity: Cardiac function/myocardial toxicity in patients suffering from highly active relapsing multiple sclerosis)** • **Cancer of white blood cells (acute myeloid leukaemia, AML) and a bone marrow disorder that causes abnormally shaped blood cells and leads to leukaemia (myelodysplastic syndrome) (Risk on haematotoxicity: Secondary acute myeloid leukaemia and myelodysplastic syndrome in patients suffering from highly active relapsing multiple sclerosis)**
Risk minimisation measure(s): Educational material
Objective and rationale The aim of the risk minimisation measures is to increase the awareness of the risks and proposed risk minimisation measures including the maximum lifetime additive dose and the monitoring requirement prior, during and after mitoxantrone treatment.
Summary description of main additional risk minimisation measures: Cardiac function/myocardial toxicity in patients suffering from highly active relapsing multiple sclerosis

Objective and rationale:
To understand risk of myocardial toxicity – recommended risk minimisation measures
Proposed action:
Healthcare professional (HCP) and patient material (consisting of HCP guide, HCP checklist, Patient guide, Patient alert card), creating awareness of importance of additive life-time dose 72 mg/m^2, monitoring of the fraction of blood ejected from a ventricle of the heart with each heartbeat (left ventricular ejection fraction) prior, during and yearly for up to 5 years after therapy, monitoring of sign and symptoms

Secondary acute myeloid leukaemia and myelodysplastic syndrome toxicity in patients suffering from highly active relapsing multiple sclerosis
Objective and rationale:
To understand risk of secondary malignancy – recommended risk minimisation measures
Proposed action:
HCP and patient material (consisting of HCP guide, HCP checklist, Patient guide, Patient alert card) to increase awareness of monitoring of blood counts, signs and symptoms

III.1.6. Planned post authorisation development plan

List of studies in post authorisation development plan				
Study/activity (including study number)	**Objectives**	**Safety concerns /efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
Prescriber survey entitled: "Mitoxantrone for the treatment of patients with highly active relapsing multiple sclerosis associated with rapidly evolving disability" (category 3)	To evaluate the Prescribing physician's awareness to risk minimisation measures in patients with highly active relapsing multiple sclerosis	cardiotoxicity (i.e. deterioration of LVEF, congestive heart failure) and haematotoxicity (i.e. secondary acute myeloid leukaemia and myelodysplastic syndrome in patients with highly active relapsing multiple sclerosis	planned	Submission date of the final study report to be agreed with the RMS.

Studies which are a condition of the marketing authorisation

Not applicable

III.1.7. Summary of changes to the Risk Management Plan over time

Not applicable