## 5.2 Part VI.2 Elements for a Public Summary

### 5.2.1 Part VI.2.1 Overview of disease epidemiology

**Metastatic (cancer that spreads to other body parts) Breast cancer**

Breast cancer is the most common cancer in women both in developed and less developed world. Global Health Estimates, 2013 estimated that worldwide over 508,000 women died in 2011 due to breast cancer. Although it is thought to be a disease of the developed countries, almost 50% of breast cancer cases and 58% of deaths occur in less developed countries. Incidence rate (number of new cases per population at risk in a given time period) in Western Europe is 89.7 per 100,000 women [WHO, 2016].

Approximately 6-10% of new breast cancer cases are initially Stage IV (advanced) or metastatic. This is sometimes called "de novo" metastatic disease, meaning from the beginning. For 2012 this means new cases of Stage IV were in the range of 13,776-22,096.

The number of metastatic recurrences are unknown, but are estimated to range between 20-30% of all existing breast cancer cases [MBCN, 2016].

**NHL (cancer that starts in cells called lymphocytes, part of the body's immune system)**

Worldwide, nearly 386,000 new cases of NHL were estimated to have been diagnosed in 2012, with incidence rates varying across the world. 1 in 48 men and 1 in 58 women are estimated to be diagnosed with NHL during their lifetime. In Europe, around 93,500 new cases of NHL were estimated to have been diagnosed in 2012.

According to statistics from the United Kingdom (UK), NHL is the sixth most common cancer and accounted for 4% of all new cases in 2013. It is the sixth most common cancer in males and the seventh most common cancer in females, with around 7,300 and 6,200 cases diagnosed respectively in 2013. Around half (49%) of NHL cases each year are diagnosed in people aged 70 and above. Over the last decade, NHL incidence rates have increased by almost a fifth (18%), with a similar increase in males (18%) and females (17%) [CRUK, 2016].

**Adult acute non-lymphocytic leukemia/ AML (type of blood cancer where too many white blood cells are produced)**

AML is generally a disease of older people and is uncommon before the age of 45. The average age of a patient with AML is about 67 years. AML is slightly more common among men than women, but the average lifetime risk in both sexes is less than half of 1% [ACS, 2016].

According to statistics from UK there were around 2,900 new cases of AML in 2013, accounting for less than 1% of all new cases. There were around 1,700 and 1,200 cases of AML diagnosed respectively in males and females in 2013. Almost 55% of AML cases each year are diagnosed in people aged 70 years and above. Over the last decade, AML incidence rates have increased by 7% in the UK, though this includes an increase in males (8%) and stable rates in females [CRUK (AML), 2016].

**Prostate cancer**

Prostate cancer is cancer of a small gland that's located below the urinary bladder and makes the fluid part of semen. It is now most common cancer in men in UK [CRUK (prostate cancer), 2016] and united states, after skin cancer and is second leading cause of cancer death in men [NIH, 2016]. Across UK, about 1 in 8 men will get prostate cancer at some point in their lives, over 47,000 men are diagnosed with prostate cancer every year and over 330,000 men are living with and after prostate cancer [PCUK, 2016]. Age and family history are significant risk factors. 99% of men diagnosed with prostate cancer are over 50 and 75% are over 70 years of age. It is more common in black men than white or Asian men [CRUK (prostate cancer), 2016]. Prostate cancer often has no early symptoms; advanced prostate cancer can cause urinary symptoms [NIH, 2016].

**Highly active relapsing MS associated with rapidly evolving disability**

MS is an immune-mediated inflammatory disease (auto-immune) that attacks the central nervous system. MS is divided into the following categories, principally on the basis of clinical criteria, including the frequency of clinical relapses, time to disease progression, and lesion development: 1. Relapsing-remitting MS: Approximately 85% of cases, 2. Secondary progressive MS 3. Primary progressive MS 10% of cases (no indication for Mitoxantrone) 4. Progressive-relapsing MS about 5%. Worldwide, approximately 2.1 million people are affected by MS. MS is more common in women. MS is usually diagnosed in persons aged 15-45 years; however, it can occur in persons of any age. The disease is seen in all parts of the world and in all races. In general, the prevalence of MS tends to increase with latitude (eg, lower rates in the tropics, higher rates in northern Europe [Luzzio c, et al, 2016].

### 5.2.2 Part VI.2.2 Summary of treatment benefits

Mitoxantrone, a cytotoxic drug that kills cancer cells, is active alone and in combination with other anticancer drugs against breast cancer, leukemia (cancer of white blood cells), and lymphoma (cancer of infection-fighting cells of the immune system, called lymphocytes). The drug is effective in treatment of prostate gland (small walnut-shaped structure which produces fluid that nourishes and protects sperm) cancer and in MS .

Mitoxantrone's effectiveness has been established against fast-growing lymphomas, like diffuse large-cell lymphomas (a type of lymphoma). In studies involving follicular lymphoma (a type of lymphoma) patients, mitoxantrone at 14-18 mg/m² every 3 to 4 weeks yielded responses in previously treated patients (including those who received doxorubicin). Patients with either relapsed (disease which returns after treatment) or refractory (disease does not respond to treatment) aggressive lymphoma responded to lower doses of mitoxantrone (12 to 14 mg/m² every 3 to 4 weeks).

Mitoxantrone, in combination with fludarabine (anticancer drug) and with or without corticosteroids, drugs that suppress inflammation (dexamethasone), is efficacious in

previously untreated patients and those with recurrent or refractory follicular lymphoma disease. Mitoxantrone combination is effective in elderly and usually well tolerated in terms of non-hematologic toxicity (not related to toxic effects of blood and its components). In patients with diffuse aggressive lymphoma, treatment with mitoxantrone, 12 mg/m², has shown similar efficacy when substituted for doxorubicin, 50 mg/m², because of its high level of activity in NHL and the potential for reduced non-hematologic toxicity.

High doses of mitoxantrone (60 to 90 mg/m²) in combination with other anticancer drugs was successfully administered to lymphoma patients as regimen for stem cell (cells that have capacity to develop into different cell types) transfer to re-establish bone marrow (a part of bone that produces blood cells) function [Armitage JO, 2002].

### 5.2.3 Part VI.2.3 Unknowns relating to treatment benefits

Data for use of mitoxantrone in various combinations for NHL are currently limited.

There is limited efficacy data in the adjuvant (supportive) treatment of breast cancer.

Efficacy in pediatric population has not been established.

## 5.2.4 Part VI.2.4 Summary of safety concerns

**Table 5-5 Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Drug induced changes affecting the heart's function leading to heart damage/drug induced damage to heart muscle.<br>(Cardiac function changes/myocardial toxicity) | Breathlessness (including breathlessness at night), cough, fluid retention (swelling) in the ankles or legs, heart fluttering (irregular heart beat), chest pain, may occur either during or months to years after therapy with mitoxantrone.<br><br>Mitoxantrone may damage heart and cause deterioration of 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:<br>• if they heart is not working well;<br>• if they had prior treatment of the chest with radiation;<br>• if they already use other medicines that affect your heart;<br>• if they had previous therapies with anthracyclines or anthracenediones (class of drugs used in cancer treatment), such as daunorubicin or doxorubicin.<br><br>The most serious side effect of mitoxantrone is damage to the heart muscle (myocardial toxicity).<br><br>Side effects associated with mitoxantrone in patients being treated for cancer: CHF (severe condition where the heart cannot anymore pump enough blood), heart attack and shortness of breath are common side effects, irregular heart beat or slowed heartbeat, abnormal electrocardiogram, reduction of the volume of blood that the left chamber (ventricle) can pump, with no symptoms and swelling (edema) are uncommon side effects and damages to the heart muscle preventing it from pumping | Patients should talk to their doctor or, pharmacist or nurse before using mitoxantrone if experienced any of the mentioned symptoms or if they already use other medicines that affect their heart.<br><br>Patients should inform their doctor or pharmacist or nurse immediately if they get any of the mentioned signs or symptoms during treatment with mitoxantrone:<br><br>Doctor should perform heart function tests before patients start mitoxantrone and at regular intervals during therapy. If patients receive mitoxantrone to treat MS doctor should test their heart function before the start of therapy, prior to each subsequent dose and yearly for up to 5 years after the end of therapy.<br><br>Patients should inform their doctor or pharmacist if they are using, have recently used or might use any other medicines. It is particularly important that they mention medicines which may increase the risk of side effects with mitoxantrone including medicines that can damage heart (e.g. anthracyclines). |

| Risk | What is known | Preventability |
|---|---|---|
| | properly (cardiomyopathy) is a rare side effect of mitoxantrone.<br><br>Side effects associated with mitoxantrone in patients being treated for MS: irregular heartbeat, abnormal electrocardiogram (abnormal result of heart function test), reduction of the volume of blood that the left ventricle can pump, with no symptoms are common side effects; CHF (severe condition where the heart cannot anymore pump enough blood), cardiomyopathy (damages to the heart muscle preventing it from pumping properly), slowed heartbeat, and heart attack are uncommon side effects of mitoxantrone. | |
| Drug induced cancer of the blood in which the bone marrow (the spongy tissue inside the large bones) makes too many white blood cells (AML) and a bone marrow disorder that causes abnormally shaped blood cells and leads to blood cancer (leukemia)<br>[Secondary AML and MDS] | A group of anticancer medicines (topoisomerase II inhibitors), including mitoxantrone, may cause the following diseases when used alone but especially in combination with other chemotherapy and/or radiotherapy:<br>• cancer of white blood cells (AML)<br>• a bone marrow disorder that causes abnormally shaped blood cells and leads to leukemia (MDS)<br><br>These are uncommon side effects of mitoxantrone. | Patients should inform their doctor or pharmacist if they are using, have recently used or might use any other medicines. It is particularly important that they mention medicines which may increase the risk of side effects with mitoxantrone including Topoisomerase II inhibitors (a group of anticancer medicines including mitoxantrone) in combination with other chemotherapy and/or radiotherapy. |
| Decrease in production of blood cells responsible for providing immunity (white blood cells), carrying oxygen (red blood cells), and/or those responsible for normal blood clotting (platelets)<br>(Bone marrow suppression) | Myelosuppression (reduced activity of the bone marrow) is one of the most serious side effects of mitoxantrone.<br><br>Side effects associated with mitoxantrone in patients being treated for cancer: reduced activity of the bone marrow (Bone marrow can be more depressed or be depressed for a longer period if you patient had chemotherapy or radiotherapy, cancer treatment with drugs and radiation) and insufficient production of bloods cells in the bone marrow (bone marrow failure) are uncommon | Patients should talk to their doctor or, pharmacist or nurse before using mitoxantrone if their bone marrow is not working well (is depressed) or if they are in generally poor health.<br><br>Patients should inform their doctor or pharmacist if they are using, have recently used or might use any other medicines. It is particularly important that they mention medicines which may increase the risk of side effects with mitoxantrone including medicines that |

| Risk | What is known | Preventability |
|---|---|---|
| | side effects; low number of red blood cells which can cause a feeling of tiredness and shortness of breath (anemia) and patients may require a blood transfusion, and low number of a special form of white blood cells (neutrophils and leukocytes) are very common side effects; Low level of platelets – which may cause bleeding or bruising, is a common side effect of mitoxantrone.<br><br>Side effects associated with mitoxantrone in patients being treated for MS: anemia (low number of red blood cells which can cause a feeling of tiredness and shortness of breath), granulocytes (low number of special white blood cells), and leukocytes (abnormal number of white blood cells) are common side effects; bone marrow failure (insufficient production of blood cells in the bone marrow), reduced activity of the bone marrow (Patient's bone marrow can be more depressed or be depressed for a longer period if have had chemotherapy or radiotherapy), low level of platelets which may cause bleeding or bruising and neutrophils (low number of special white blood cells) are uncommon side effects effect of mitoxantrone. | suppress the bone marrow's production of blood cells and platelets (myelosuppressive agents).<br><br>If patients of breast cancer or NHL (a form of lymphnode cancer) have low bone marrow reserves, they should receive a lower first dose of 12 mg per square metre. Their doctor should decide exactly what further doses they need. This will depend on how much and for how long the activity of bone marrow is decreased (suppressed).<br><br>When mitoxantrone is used in combination with other anticancer drugs (e.g. cytarabine, etopiside) to treat AML their doctor should decide exactly what dose of each medicine should be given. The dose may have to be adjusted if the combination of drugs causes more suppression of bone marrow than mitoxantron alone. |
| Abnormal development of an unborn child/ hazard associated with some chemical substances, that they will interfere in some way with normal reproduction<br>(Teratogenicity/reproductive toxicity) | Mitoxantrone may cause risks to the unborn child, if this medicine is used during pregnancy or if patients become pregnant while taking this medicine.<br>This medicine might increase the risk for transitory or persistent absence of menstruation (amenorrhea) in women of childbearing age. | Patients should talk to their doctor or, pharmacist or nurse before using mitoxantrone if they are pregnant or if they and their partner are trying to become pregnant. When used for treatment in other indications mitoxantrone should not be administered during pregnancy in particular during the first trimester of pregnancy.<br><br>Men must not father a child and should use contraceptive measures during and at least 6 months after therapy. Women |

| Risk | What is known | Preventability |
|---|---|---|
| | | of childbearing potential should have a negative pregnancy test prior to each dose, and use effective contraception during therapy and for at least 4 months after cessation of therapy. If this medicine is used during pregnancy or if patients become pregnant while taking this medicine, the doctor should be informed and while taking mitoxantrone, the patient should be informed of the potential risk to the fetus and genetic counselling should be provided.<br><br>Because of the risk of amenorrhea a patient should talk to her doctor if she is planning to become pregnant in the future; as her eggs may need to be frozen. |
| A condition that can occur after treatment of a fast-growing cancer wherein the cancer cells die, break apart and release their contents into the blood leading to a change in certain chemicals in the blood, which may cause damage to organs, including the kidneys, heart, and liver.<br>(Tumor lysis syndrome) | Cases of tumor lysis syndrome were reported with the use of mitoxantrone.<br><br>Metabolic disturbances (tumor lysis syndrome) is uncommon side effect of mitoxantrone | Patient's electrolyte levels, uric acid, and urea levels should be carefully monitored. |

**Table 5-6 Important potential risks**

| Risk | What is known |
|---|---|
| Use in breast-feeding women | Mitoxantrone is secreted into breast-milk and may cause serious side effects to the baby. Therefore, patient is advised not to breast-feed while using mitoxantrone and for up to one month after the last administration of the drug and if the patient is already breast-feeding, patient must be advised to stop breast-feeding before taking mitoxantrone<br><br>Patient is advised not to use mitoxantrone while breast-feeding and should ask the doctor or pharmacist for advice before taking this medicine. |

**Table 5-7 Missing information**

None

### 5.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other HCPs with details on how to use the medicine, the risks and recommendations for minimizing 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 minimization measures.

This medicine has following additional risk minimization measures related to the use of mitoxantrone in the treatment of MS.

**Table 5-8 Cardiac function changes/myocardial toxicity**

| **Risk minimization measures** |
|---|
| **Summary description of main additional risk minimization measures:**<br><br>Prescriber guide, Checklist for HCP, Patient guide and Patient alert card<br><br>**Objective and rationale:**<br><br>To remind HCP of the importance of recognizing the risk of cardiotoxicity and AML and the need to instruct patients on correct identification of signs and symptoms they need to look out for and what action are needed to be taken.<br><br>**Proposed action:**<br><br><u>HCP Brochure:</u><br>Mitoxantrone could cause cardiotoxicity<br>• signs and symptoms<br>• the need for echocardiogram or multiple-gated acquisition (MUGA) evaluation of the left-ventricular ejection fraction (LVEF) prior to administration of each dose and yearly for up to 5 years after the end of therapy.<br><br>Mitoxantrone could cause hematotoxicity, including secondary acute myeloid leukemia and myelodysplastic syndrome<br>• signs and symptoms<br>• the need for monitoring at the start and prior to each treatment administration<br><br><u>Checklist for HCP</u><br>The Checklist for Prescribers encourages the HCP to use this tool in conjunction with the SmPC during every mitoxantrone consultation. The HCP should be reminded to evaluate the LVEF, the lifetime maximum dose and a full blood count platelets. The patients should be informed about the risk of heart problems and blood cancer and the situations when these risks are increased.<br><br><u>Patient guide</u> |

| Risk minimization measures |
|---|
| • signs and symptoms of cardiotoxicity and hematotoxicity<br>•<br>•<br>• Information on the need of regular monitoring, and when it should be carried out, for cardiotoxicity and hematotoxicity<br><br>Patient Alert Card<br>• key signs and symptoms regarding cardiotoxicity and hematotoxicity |
| |

**Table 5-9 Secondary AML and MDS**

| Risk minimization measures |
|---|
| **Summary description of main additional risk minimization measures:**<br><br>Prescriber guide, Checklist for HCP, Patient guide and Patient alert card<br><br>**Objective and rationale:**<br><br>To remind HCP of the importance of recognizing the risk of cardiotoxicity and AML and the need to instruct patients on correct identification of signs and symptoms they need to look out for and what action are needed to be taken.<br><br>**Proposed action:**<br><br>HCP Brochure:<br>Mitoxantrone could cause cardiotoxicity<br>• signs and symptoms<br>• the need for echocardiogram or multiple-gated acquisition (MUGA) evaluation of the left-ventricular ejection fraction (LVEF) prior to administration of each dose and yearly for up to 5 years after the end of therapy.<br><br>Mitoxantrone could cause hematotoxicity, including secondary acute myeloid leukemia and myelodysplastic syndrome<br>• signs and symptoms<br>• the need for monitoring at the start and prior to each treatment administration<br><br>Checklist for HCP<br>The Checklist for Prescribers encourages the HCP to use this tool in conjunction with the SmPC during every mitoxantrone consultation. The HCP should be reminded to evaluate the LVEF, the lifetime maximum dose and a full blood count platelets. The patients should be informed about the risk of heart problems and blood cancer and the situations when these risks are increased. |

| **Risk minimization measures** |
|---|
| Patient guide<br>• signs and symptoms of heart problems and blood cancer<br><br>• Information on the need of regular monitoring, and when it should be carried out, for cardiotoxicity and hematotoxicity<br><br>Patient Alert Card<br>• key signs and symptoms regarding cardiotoxicity and hematotoxicity |

### 5.2.6 Part VI.2.6 Planned post authorization development plan

None

### 5.2.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

N/A (first submission)