PART VI SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY MEDICINAL PRODUCT

VI.1 Elements for summary tables in the European Public Assessment Report (EPAR)

VI.1.1 Summary table of safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Severe myelosuppression associated with increased susceptibility to severe infections and haemorrhages • Secondary leukaemia • Effects on fertility • Co-administration with nalidixic acid in children • Gastrointestinal toxicity • Pulmonary toxicity
Important potential risks	• Medication/ dispensing error • Safety in patients with renal impairment • Use in patients with alcoholism, liver disease or epilepsy
Missing information	• Exposure during pregnancy and lactation • Use in paediatric patients • Use in elderly

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable

VI.1.4 Summary table of risk minimisation measures

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
Hypersensitivity	The risk of hypersensitivity associated with use of the drug product is described in the SPC Sections 4.3, 4.4, 4.8 and PIL Sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Severe myelosuppression associated with increased susceptibility to severe infections and haemorrhages	The risk of severe myelosuppression associated with increased susceptibility to severe infections and haemorrhages associated with (i) use of the drug product (ii) overdose of the drug product is described in the SPC Sections 4.3, 4.4, 4.5, 4.8, 4.9 and PIL Sections 2 and 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Secondary leukaemia	The risk of secondary leukaemia associated with use of the drug product is described in the SPC Sections 4.4, 4.8, 5.3 and PIL Section 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Effects on fertility	The risks associated with use of the drug product on fertility is described in the SPC Section 4.4, 4.8. 5.3 and PIL Section 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Co-administration with nalidixic acid in children	The risk associated with co-administration of the drug product with nalidixic acid in children is described in the SPC Section 4.5 and PIL Section 2	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	and appropriate advice is provided to the prescriber to minimise this risk.	
Gastrointestinal toxicity	The risk of gastrointestinal toxicity associated with use of the drug product is described in the SPC Sections 4.8, 4.9 and PIL Section 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Pulmonary toxicity	The risk of pulmonary toxicity associated with use of the drug product is described in the SPC Section 4.8 and PIL Section 4 and appropriate advice is provided to the prescriber to minimise this risk.	None
Important Potential Risks		
Medication/ dispensing error	The risk of medication/ dispensing error associated with use of the drug product is described in the SPC Sections 4.2 and PIL Section 3 and appropriate advice is provided to the prescriber to minimise this risk.	None
Safety in patients with renal impairment	The risks associated with use of drug product (i) at conventional dose in patients with renal impairment and (iii) at high dose in patients with renal impairment are described in the SPC Sections 4.2, 4.4, 4.8 5.2 and PIL Sections 2, 3, 4 and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with alcoholism, liver disease or epilepsy	The risks associated with use of the drug product in patients with alcoholism, liver disease or	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	epilepsy are described in the SPC Section 4.4 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	
Missing Information		
Exposure during pregnancy and lactation	The SPC Sections 4.3, 4.4, 4.6, 5.3 and PIL Section 2 clearly melphalan should not be used during pregnancy, especially during the first trimester. Mothers receiving melphalan should not breastfeed.	None
Use in paediatric patients	The SPC Sections 4.2, 4.4 and PIL Section 3 mention that there is no adequate experience for children.	None
Use in elderly	The SPC Sections 4.2, 5.2 clearly mention that although melphalan is frequently used at conventional dosage in the elderly, there is no specific information available relating to its administration to this patient sub-group. Experience in the use of high dose melphalan in elderly patients is limited.	None

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Multiple myeloma:

Multiple myeloma is a cancer arising from plasma cells, a type of white blood cell made in the bone marrow which help to fight infections. In myeloma, these plasma cells become abnormal, multiply uncontrollably.[1] Multiple myeloma is the second most common blood related cancer and is responsible for at least 2 out of 100 cancer-related deaths.[2] Approximately 84,000 people in Europe

have myeloma.[1] In Europe, the occurrence of multiple myeloma is 4.5 to 6.0 in 100,000 every year with a death rate of 4.1 in 100,000 every year.[2] In UK, around 4,800 new cases of multiple myeloma are diagnosed each year.[3] Black people, Pacific Islanders, and Maori in New Zealand have a reported high occurrence of multiple myeloma, followed by Europeans and North American white people. Low occurrence rates have been reported for Asians living in Asia (Chinese, Indian, Japanese, and Filipino populations) and the US.[2]

Ovarian cancer:

Ovarian cancer refers to cancer of the cells of the ovary (female organ which release eggs). It is the seventh most common cancer worldwide for females, and the 18th most common cancer overall, with nearly 239,000 new cases diagnosed in 2012 and fifth most common cancer in Europe for females, and the 13th most common cancer overall, with around 65,600 new cases diagnosed in 2012. A total of 7,284 new cases of ovarian cancer were reported in 2013 in UK.[4] In the UK, around 7,100 women are diagnosed with ovarian cancer each year. Overall, 72 out of every 100 women will live for at least one year after being diagnosed with ovarian cancer. Around 46 out of 100 women will live for at least five years, and about 35 out of 100 will live for at least 10 years. However, women with advanced ovarian cancer have a poorer survival rate.[5]

Neuroblastoma:

Neuroblastoma is a type of cancer that starts in certain very early forms of nerve cells found in an unborn child. The term neuro refers to nerves, while blastoma refers to a cancer that affects immature or developing cells. This type of cancer occurs most often in newborns and young children.[6] It is the most common cancer in newborns less than 1 year old accounting for one fifth of cancers in this age group.[7] It is rarely found in children older than 10 years.[6] It accounts for about 6 out of 100 cases of all cancers in children, with around 95 diagnosis every year. It affects 100 children each year in the UK. It is slightly more common in boys than in girls. Neuroblastoma has one of the lowest survival rates of all childhood cancers, with only 67 out of 100 patients surviving to five years.[7]

Malignant melanoma:

Melanomas are common cancers of the skin. Malignant melanoma is the 19th most common cancer worldwide with around 232,000 new cases diagnosed in 2012. Malignant melanoma is the ninth most common cancer in Europe, with more than 100,000 new cases diagnosed in 2012 accounting 3 out of 100 of the total cases of cancer. It is the fifth most common cancer in the UK in 2013 accounting for 4 out of 100 all new cases.[8] European populations (e.g., the UK, Germany, Netherlands, Austria, France) reported melanoma rates in the range 4–10 in 100,000 people every year.[9] Highest occurrence rates occur in older males and females.[8] It is the 19th most common cause of cancer death in Europe, with around 22,200 deaths from malignant melanoma in 2012 accounting for 1 in 100 total deaths.[10]

Soft tissue sarcoma:

Soft tissue sarcomas are a group of rare cancers affecting the tissues that connect, support and surround other body structures and organs. Tissues that can be affected by soft tissue sarcomas include fat, muscle, blood vessels, deep skin tissues, tendons and ligaments. Soft tissue sarcomas can develop in almost any part of the body, including the legs, arms and the trunk.[11] Soft-tissue sarcomas affect around 1 out of 100 all adult cancer cases and 15 out of 100 children cases. Adult soft-tissue

sarcomas are rare, with an estimated occurrence of 4 in 100,000 every year in Europe.[12] Occurrence of soft tissue sarcomas ranges from 3.3 in 100,000 in Eastern Europe to 4.7 in 100,000 in Northern Europe.[13] Soft tissue sarcomas account for around one in every 100 cancers diagnosed in the UK. More than 3,000 new cases are diagnosed every year.[11]

VI.2.2 *Summary of treatment benefits*

Multiple myeloma:

- In a study, effectiveness and safety of three-drug combination of melphalan, prednisone, and thalidomide (MPT) has been studied in 21 patients with multiple myeloma. Treatment consisted of 4-week cycles of melphalan and prednisone on days 1-7, with thalidomide given daily. It is concluded that MPT is an effective first-line treatment option for patients with multiple myeloma, including elderly patients.[14]
- In another study, melphalan + dexamethasone was found to be safe and effective in 34 patients with multiple myeloma who were not eligible for transplantation that uses person's own stem cells (autologous stem cell transplantation).[15]
- The results from the study involving 42 patients with newly diagnosed multiple myeloma showed that bortezomib + melphalan + prednisone was safe and effective in older patients having recurrence of multiple myeloma.[16]

Ovarian cancer:

The effectiveness of melphalan was studied in 33 female patients with advanced ovarian cancer. The treatment schedule was repeated every 28 days for a maximum of 6 cycles. It was concluded that melphalan administered over a 24-h period in ovarian cancer patients appeared to provide some clinical benefits.[17]

Neuroblastoma:

In a study, the impact of high dose melphalan as a single agent in patients with stage III and IV neuroblastoma was evaluated in 167 children. Patients received treatment with other anticancer medicines and after surgical excision of tumour, patients received high-dose melphalan. In this study, high dose melphalan improved the length of event free survival and overall survival of children with stage IV neuroblastoma.[18]

Malignant melanoma:

In a study, total 173 isolated limb perfusion (ILP- a procedure used to deliver anticancer drugs directly to an arm or leg) carried out in patients with multiple melanoma of the limb. Patients received TNF-α (anticancer drug) in the arm or in the leg. Melphalan was given 30 minutes after the limb temperature reached 38–39.5ºC. Study demonstrated that TNF-α and melphalan-ILP is a safe and effective treatment for melanoma patients.[19]

Soft tissue sarcoma:

In a study, 49 patients with soft tissue sarcoma of an extremity undergoing ILP with TNF-α and melphalan were included. Melphalan was given in the upper and lower limb. The five-year disease specific survival rate was 48% for 49 patients. In conclusion, a 63% overall tumor response rate and a 57% local control rate with limb preservation was achieved.[20]

VI.2.3 Unknowns relating to treatment benefits

The safety and effectiveness of melphalan in children has not been established. Melphalan is frequently used at normal dosage in older patients; however, there is no specific information available relating to its administration in these patients.

VI.2.4 Summary of safety concerns

Important Identified Risks

Risk	What is known	Preventability
Allergic reactions (hypersensitivity)	Signs of allergic reaction may include a rash, lumps or hives on the skin; swollen face, eyelids or lips; sudden wheeziness and tightness of the chest and collapse (due to condition in which the heart suddenly and unexpectedly stops beating). There have been reported cases of heart attack associated with severe allergic reactions. Skin rashes including blotchy lesions and itching skin are rare (affects less than 1 in 1,000 users) side effects reported with melphalan use.	Melphalan should not be used in patients allergic to melphalan or any of the other contents of Melphalan solution for injection/infusion including propylene glycol. If patients are not sure about allergy to medicinal product, they should speak with their doctor or nurse before having melphalan. If patients develop any sign of allrgic reaction, they should talk to their specialist doctor or go to hospital straight away.
Serious decrease in bone marrow activity associated with increase vulnerability to develop infections and bleeding (severe myelosuppression associated with increased susceptibility to severe infections and haemorrhages)	A drop in the number of blood cells and platelets is a very common (affects more than 1 in 10 users) side effect reported with melphalan use. Changes in red blood cell count due to increased breakdown of the red blood cells (haemolytic anemia - which can lead to tiredness, fever, dizziness and increase infections) is a rare (affects less than 1 in 1000 users) side-effect with use of melphalan. Overdose of melphalan will lead to drop in the number of blood cells. Vaccination using a live organism vaccine has the potential to cause infection in patients with weak immune	Melphalan should not be used in patients with severe myelosuppression. Melphalan should be used with care in patients who have undergone radiotherapy (use of radiation to treat illeness) or chemotherapy (type of cancer treatment that uses medicines to destroy cancer cells) as there are chances of increased harmful effects on bone marrow. When blood count continues to fall after treatment is stopped, so at the first sign of an abnormally large fall in white blood cells or platelet counts, treatment should be temporarily interrupted. When patients are given Melphalan, their doctor will

	system. Some vaccines (like polio, measles, mumps and rubella) may cause an infection if the patient gets vaccinated while being treated with Melphalan.	take regular blood tests. This is to check the number of cells in blood. The doctor may sometimes change the dose as a result of these tests. Patients should inform their doctor, pharmacist or nurse if they have had radiotherapy or chemotherapy, now or recently. If patients develop any unexpected bruising or bleeding or feeling extremely tired, dizzy or breathless (as this could mean that too few blood cells of a particular type are being produced), they should talk to their specialist doctor or go to hospital straight away.Vaccinations with live organism vaccines are not advised in patients with weak immune system. Patients should tell their doctor, pharmacist or nurse if they are going to have vaccination or were recently vaccinated with live organisms before using Melphalan. In case of overdose with melphalan, general supportive measures, together with appropriate blood and platelet transfusions, should be done if necessary and consideration given to hospitalisation, antibiotic therapy and use of medicines which can raise blood count.
Cancer of the blood forming tissues(secondary leukaemia)	Melphalan has been reported to cause cancer of the blood-forming tissue, usually the bone marrow. It result in high numbers of abnormal white blood cells. Acute leukemia (a blood cancer) has been reported as a	The risk of causing cancer of blood must be balanced against the therapeutic benefit when considering the use of melphalan.

	common (affects less than 1 in 10 users) side effect. Acute leukemia may occur, generally after a long period of time after treatment has ended, and particularly in the older people after long-term use in combination therapy and radiotherapy. Cancer of bone marrow that starts quickly (acute myeloid leukaemia) and a group of cancers in which immature blood cells in the bone marrow do not mature or become healthy blood cells (myelodysplastic syndromes) have been reported with not known frequency with use of melphalan..	
Effect of melphalan on ability to reproduce (effects on fertility)	Temporary and permanent infertility (inability to produce child) with reduction in the number of motility of the sperm in semen (azoospermia) and loss of menstrual periods (amenorrhoea) have been reported as common side effects (may affect less than 1 in 10 patients) with melphalan.Melphalan causes decrease in function of ovaries in women immediately before the time of stopping of menstruation resulting in absence of menstruation (amenorrhoea) in a significant number of patients. Melphalan can have harmful effects on sperms and may cause temporary or permanent sterility (inability to produce child) in male patients.	Patients should inform their doctor if their periods stop. . Patients (male as well as female) should not take Melphalan if they are planning to have a baby. Males who have female partners who are able to become pregnant should use effective birth control during and after treatment with Melphalan. Male patients who are treated with melphalan are advised not to produce a child during the treatment with melphalan and up to 6 months afterwards and to consult a sperm reserve before starting treatment. Patients should contact their doctor for advice about how long to use birth control after treatment with melphalan.

Simultaneous use of the medicinal product with nalidixic acid in children (co-administration with nalidixic acid in children)	Nalidixic acid is an antibiotic used to treat urinary tract infections. Nalidixic acid together with high-dose intravenous melphalan has caused deaths in children due to inflammation of small and large intestine (haemorrhagic entercolitis).	Patients should tell the treating doctor or nurse if they are taking or have recently taken nalidixic acid.
Harmful effects on gut (gastrointestinal toxicity)	Mouth ulcers (inflammation of mouth/ stomatitis) at high doses and feeling sick (nausea), being sick (vomiting), loose stools (diarrhoea) are very common (affects more than 1 in 10 people) side effects and mouth ulcers with normal doses is a rare (affects more than or equal to 1 in 10,000 and less than 1 in 1,000 users) side effect reported with melphalan use.	If patients develop any of the harmful effects on gut, they should talk to their treating doctor or go to hospital straight away. Prior treatment with cyclophosphamide (medicine mainly used for cancer treatment) appears to reduce the severity of harmful effects on gut induced by high-dose melphalan.
Harmful effects to lungs (pulmonary toxicity)	Interstitial pneumonia and pulmonary fibrosis are the lung problems which may make the patients cough or wheeze and make it difficult to breathe. Lung infections (pneumonia) and lung damage caused by changes in the lung tissue (pulmonary fibrosis, including those with death) are rare (affects less than 1 in 1,000 users) side effects reported with melphalan use.	If patients develop any sign suggestive of lung problems which may make them cough or wheeze and it becomes difficult to breathe, they should talk to their treating doctor or go to hospital straight away.

Important Potential Risks

Risk	What is known
Inappropriate use or distribution of the medicine (medication/ dispensing error)	Melphalan should only be prescribed for patients by a specialist doctor who is experienced in treating blood problems or cancer. Melphalan solution has limited stability and should be prepared

	immediately before use. Any solution unused after 30 minutes should be destroyed according to standard guidelines for handling and disposal of anticancer drugs.
Safety in patients with kidney problems (safety in patients with renal impairment)	Removal of Melphalan from the body may be reduced in patients with kidney problems. In patients with kidney problems, dose reduction may be necessary. High levels of a chemical called urea in the blood in the early stages of treatment with melphalan – in people with kidney problems who are being treated for myeloma is a common (affects less than 1 in 10 people) side effect with Melphalan treatment. Patients should inform their doctor, pharmacist or nurse if they have a kidney problem before using Melphalan.
Use in patients with alcohol abuse, liver disease or fits (use in patients with alcoholism, liver disease or epilepsy)	This medicinal product contains 5 % ethanol (alcohol), equivalent to 10 ml beer or 2.4 ml wine which is harmful for those suffering from alcoholism. Amount of alcohol in this medicinal product should be considered in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or fits. Additionally, melphalan contains propylene glycol which may cause alcohol -like symptoms. The patients must check with their doctor before driving or operating any tools or machines because the amount of alcohol in this medicine may impair the ability to drive or use machines.

Missing Information

Risk	**What is known**
Exposure in pregnant and breast-feeding women (exposure during pregnancy and lactation)	Melphalan should not be used during pregnancy because it may cause permanent damage to an unborn child. The use of melphalan should be avoided during pregnancy, particularly during the first three months of pregnancy. The potential harmful effects to the unborn child should be considered against potential benefits to the mother. Melphalan may harm the sperm or eggs. Reliable birth control measures must be taken to avoid pregnancy while the patient or patient's partner are having this injection. And pregnancy should be avoided for at least 6 months after stoppage of the medicine. Patients should not breast-feed while having Melphalan. Patients should ask for the doctor or midwife advice while using melphalan

	during breast-feeding. This medicinal product contains 5 % ethanol (alcohol), equivalent to 10 ml beer or 2.4 ml wine which has to be taken into account in pregnant or breast-feeding women. Patients who are pregnant or breast-feeding, or think may be pregnant or are planning to have a baby, should ask their doctor for advice before taking this medicine.
Use in children (use in paediatric patients)	Melphalan at normal doses, is only rarely indicated in children and there is no adequate experience for children. Dosage guidelines cannot be stated.
Use in older people (use in elderly)	There is no specific information available relating to the use of melphalan in older people. Experience in the use of high dose melphalan in older patients is limited. Adequate performance status and organ function should be considered before using high dose melphalan in older patients.

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 Melphalan can be found in the Melphalan's EPAR page.

No additional risk minimisation measures are planned for this product.

VI.2.6 Planned post-authorisation development plan

There is no planned post – authorisation development plan for Melphalan 50 mg powder and solvent for solution for injection/infusion.

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

Major changes to the Risk Management Plan for Melphalan over time are as follows.

Version	**Date**	**Safety Concerns**	**Comment**
1.0	18 Jul 2016	**Important identified risks** • Hypersensitivity	Initial version

Version	Date	Safety Concerns	Comment
		• Bone marrow depression • Mutagenicity • Acute leukaemia • Suppression of ovarian function resulting in amenorrhoea • Fatal haemorrhagic enterocolitis in children on concomitant high-dose intravenous use with nalidixic acid • Impaired renal function on concomitant high-dose intravenous use with ciclosporin in bone marrow transplant patients **Important potential risks** • Medication error • Use in patients with renal impairment • Tumour lysis syndrome • Infection on concomitant use with live vaccines • Use in patients with alcoholism, liver disease or epilepsy • Use during pregnancy and lactation **Missing information** • Use in elderly	
1.1	23 Jan 2017	**Important identified risks** • Hypersensitivity • Severe myelosuppression associated with increased susceptibility to severe infections and haemorrhages • Secondary leukaemia • Effects on fertility • Co-administration with nalidixic acid in children • Gastrointestinal Toxicity • Pulmonary toxicity **Important potential risks**	The summary of safety concerns has been updated as suggested by RMS Day 70 Preliminary Assessment Report.

Version	Date	Safety Concerns	Comment
		• Medication/ dispensing error • Safety in patients with renal impairment • Use in patients with alcoholism, liver disease or epilepsy **Missing information** • Exposure during pregnancy and lactation • Use in paediatric patients • Use in elderly	