## VI.2 Elements for a public summary

Melphalan SUN is a medicine used in the treatment of certain forms of cancer:

- ***multiple myeloma*** (a type of cancer that develops from cells in the bone marrow called plasma cells. Plasma cells help to fight infection and disease by producing antibodies.
- ***advanced cancer of the ovaries***
- ***childhood neuroblastoma*** (cancer of the nervous system)
- ***malignant melanoma*** (skin cancer)
- ***soft tissue sarcoma*** (cancer of the muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body).

### VI.2.1 Overview of disease epidemiology

#### *Multiple myeloma*

Multiple myeloma (MM) is a relatively uncommon type of cancer accounting for about 102,000 incident cases and 72,000death cases reported annually. The cause of MM is poorly understood. It partly depends upon the risk factors such as increasing age, male gender, black race, chromosomal abnormalities, family history with familial aggregates, infections with HIV and hepatitis C virus.

In Europe, 39000 cases of myeloma were diagnosed in 2012 (1% of total cancer cases). The highest incidence rates for myeloma were observed in Norway for both men and women; the lowest rates begin found in Albania for men and Bosnia -Herzegovina for women.

#### *Advanced cancer of the ovaries*

Ovarian cancer ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system. A woman's risk of getting ovarian cancer during her lifetime is about 1 in 75. Her lifetime chance of dying from ovarian cancer is about 1 in 100. This cancer mainly develops in older women. About half of the women who are diagnosed with ovarian cancer are 65 years or older. It is more common in white women than African-American women. Following factors may increase the risk of ovarian cancer:getting older, inherited faulty genes or having breast cancer before.[4]

#### *Childhood neuroblastoma*

Neuroblastoma is a type of cancer that begins in the nerve cells outside the brain of infants and young children. It can start in the nerve tissue near the spine in the neck, chest, abdomen, or pelvis, but it most often begins in the adrenal glands located on top of both kidneys.

Neuroblastoma is found most often in children younger than 5. It is the third most common type of cancer in children in general and the most common cancer in babies younger than 1 year old. It can form before the baby is born and can sometimes be found during a prenatal (before birth) ultrasound. Most often,

neuroblastoma is found after the cancer has spread over, lungs, bones, and bone marrow, ead to other parts of the body, such as the lymph nodes.

The prevalence is about 1 case per 7,000 live births; the incidence is about 10.54 cases per 1 million per year in children younger than 15 years. About 37% are diagnosed as infants, and 90% are younger than 5 years at diagnosis, with a median age at diagnosis of 19 months.[5-6]

### *Malignant melanoma*

Melanoma is a very aggressive form of skin cancer. Only 1 % of all skin cancers are melanoma, but melanoma causes a large majority of skin cancer deaths. If it isn't diagnosed early, it is likely to invade nearby tissues and spread to other parts of the body.

The incidence of melanoma worldwide has increased 15 times in the last 40 years. Melanoma is more than 20 times more common in whites than in African Americans. Incidence rates are higher in women than in men before the age of 50, but by age 65, rates in men double those in women, and by age 80 they are triple. The risk for each person can be affected by a number of different factors such as:ultraviolet radiation from the sun or sunbeds, skin type, hair and eye colour, number of moles, family history of melanoma, certain medical conditions, including having a weakened immune system.

### *Soft tissue sarcoma*

Soft tissue sarcoma is a cancer that starts in soft tissues of the body, including muscle, tendons, fat, lymph vessels, blood vessels, nerves, and tissue around joints. The tumors can be found anywhere in the body but often form in the arms, legs, chest, or abdomen.

Soft-tissue sarcomas are relatively uncommon cancers. They account for less than 1% of all new cancer cases each year. Sarcomas account for over 20% of all childhood cancers and less than 1% of all cancers.. The risks for sarcoma are not well-understood. Risks for sarcoma development can be divided into environmental exposures, genetic susceptibility, and an interaction between the two. HIV-positive people are at an increased risk for Kaposi's sarcoma, even though HHV8 is the causative virus. Radiation exposure from radiotherapy has also been strongly associated with secondary sarcoma development in certain cancer patients.

## VI.2.2 Summary of treatment benefits

Melphalan is a type of cancer medicine known as an alkylating agent. It works by adding a small chemical group called alkyl group to the DNA in cells. DNA is the genetic code that is in the nucleus of all cells and controls everything the cell does. By altering the DNA Melphalan interfers with its function in cell division and growth. As a result, the cells cannot divide and grow and they ultimately die. The medicine acts mainly against fast growing cells, such as cancer cells.

Melphalan SUN powder for solution for injection /infusion is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Alkeran which is used to treat multiple myeloma, advanced oovarian cancers, neuroblastoma, melanoma and soft tissue sarcomas.. Beacause Melphalan SUN is a generic medicine, its benefits and risks are taken as being the same as the reference medicinal product. Studies with Melphalan SUN in people have been limited to tests to determine that it is bioequivalent to the reference medicine Alkeran (two medicines are bioequivalent when they produce the same levels of the active substance in the body).

The efficacy and safety of reference medicinal product has been studied in many large controlled clinical trials. In most of these studies, Melphalan was combined with other anticancer treatments and compared either with combinations of different treatments or with the same treatments but without Melphalan. The main measures of effectiveness were the number of patients whose cancer responded to treatment, how long the patients lived without their disease getting worse and how long the patients survived.

### VI.2.3 Unknowns relating to treatment benefits

The safety of high-doses of Melphalan in elderly patients have not been established. Melphalan exposure during pregnancy and its teratogenic potential has not been investigated in humans.

### VI.2.4 Summary of safety concerns

#### Important identified risks

| Risk | What is known | Preventability |
|---|---|---|
| | | |
| ***1. Increased rate of mutation***<br>[Mutagenicity]<br>***2.*** | Human DNA is constantly subject to mutations, accidental changes in its code. Mutations can lead to missing or malformed proteins that can lead to disease. Melphalan like other alkylating agent acts on cell's DNA and can cause mutations, chromosomal abnormalities and other DNA damage. In view of this mutagenic properties and structural similarity to known teratogenic medicines, it is possible that Melphalan could cause birth defects if used during pregnancy.<br>Melphalan was mutagenic in vivo causing chromosomal aberrations. | Yes, by<br>Being aware that Melphalan may cause chromosomal aberrations upon administration. |
| ***3. Decreased bone marrow activity***<br>[Myelosupression] | Myelosupression is a common side effect with cancer medication like Melphalan. The decreased in bone marrow activity results in to low number of blood cells such as red blood cells, white blood cells, and platelets. When myelosuppression is severe, it is called myeloablation.<br>Severe myelosuppression is more common with intravenous administration of Melphalan than with oral admisnitration. | Yes.<br>Careful hematologic monitoring (e.g. leukocyte count with differential, platelet count, hemoglobin) is required prior to and at periodic intervals during therapy (i.e., prior to each subsequent course of oral melphalan and prior to each subsequent infusion of Melphalan). |

| Risk | What is known | Preventability |
|---|---|---|
| | The lowest decreased in white cells and platelet generally occurs 2–3 weeks after treatment and recovery usually occurs 4–5 weeks after treatment. Although irreversible bone marrow depression has been reported especially at high doses.<br><br>High-dose melphalan is frequently given as part of the conditioning regimen for autologous stem cell transplantation. This should be done only under the close supervision of an expert tea able to ensure stem cell support<br><br>If severe myelosupression occurs during conventional therapy, Melphalan should be withhold until leukocyte count is >3000/mm3 and platelet count is >100,000/mm3.<br><br>Supportive care should be provide for patient who develop infections, bleeding, and symptomatic anemia. | The treating physician must check the patient's past medical history and should not recommend Melphalan in patients with compromised bone marrow reserve (i.e., prior radiation therapy or prior therapy with other cytotoxic agents)<br><br>The patients should be monitor closely for symptoms of bone marrow suppression (e.g., severe infections, bleeding, symptomatic anemia). |
| ***4. Complication due to the breakdown of cancer cells***<br><br>[Tumour lysis syndrome] | The action of Melphalan is through rapid destruction of cancer cells, however when large numbers of cancer cells are killed rapidly, it will result in tumour lysis syndrome. The signs and symptoms include muscle cramping, muscle weakness, confusion, visual loss or disturbances, shortness of breath, increased uric acid (hyperuricemia), potassium (hyperkalemia), phosphate (hyperphosphatemia) and decreased calcium (hypocalcemia) in blood. In severe form, it may lead to rapid onset of kidney failure.<br><br>Patients with high tumour burden prior to treatment are at risk of tumour lysis syndrome. | Yes.<br><br>The high risk patients should be closely monitored.<br><br>Preventative measures should be taken as necessary and treatment should be started early for identified cases. |
| ***5. Cancers***<br><br>[Malignancy]] | It is also possible that the use of Melphalan will increase the risk of developing another type of cancer called | Yes.<br><br>Patients who received therapy with Melphalan |

| Risk | What is known | Preventability |
|---|---|---|
| | secondary acute leukaemia (cancer of the blood) in the future. Secondary acute leukaemia causes bone marrow (tissue in bones that produces red and white blood cells) to produce large numbers of cells that do not work properly. Symptoms of this condition include tiredness, fever, infection and bruising. | should have regular blood tests to detected if there are large numbers of cells in blood that are not working properly and too few blood cells that are working properly. |
| | | |

## Important Potential Risks

| Risk | What is known (including reason why it is considered a potential risk) |
|---|---|
| | |
| ***6. Stomach and bowel toxicities including bloody diarrhea***<br>[Gastrointestinal toxicities including haemorrhagic enterocolitis when used in combination with Nalidixic acid] | Gastrointestinal disturbances such as nausea, vomiting and diarrhoea are very common. At high doses of Melphalan stomatitis (mouth and lips inflammation) is very common. The incidence of diarrhoea, vomiting and stomatitis becomes the dose limiting toxicity in patients given high intravenous doses of Melphalan in association with heamopoietic stem cell rescue. Cyclophosphamide pre-treatment appears to reduce the severity of gastrointestinal damage induced by high-dose of M.<br>When nalidixic acid (an antibiotic used to treat urinary tract infections) and Melphalan are given simultaneously, the incidence of severe hemorrhagic necrotic enterocolitis has been reported to increase in children. Haemorrhagic enterocolitis is characterized by inflammation of the small and large bowel mucosa, that can cause abdominal pain and bloody diarrhoea and in severe form the bowel mucosa can undergo necrosis (tissue death). |
| ***7. Reduce rate of drug removal from the body in patient with kidney impairment***<br>[Decreased clearance in patients with renal impairment ] | The rate of Melphalan removal from the body is decreased in patients with kidney impairment. In the early stages of Melphalan therapy a temporary significant elevation of the blood urea has been seen in patients with renal damage. Therefore, dosage reduction of up to 50% should be considered in patients with moderate to severe kidney impairment and subsequent dosage determined according to the degree of bone marrow suppression. |
| | |

## Missing Information

| Risk | What is known |
|---|---|
| ***8. Limited information on the use in old patients***<br>[Use in elderly patients] | Clinical experience with Melphalan has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased liver, kidney or heart function. |
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### VI.2.5 Summary of risk minimisation activities 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).

For all of the above mentioned risks, the routine risk minimisation measures as presented in proposed SmPC and PL of Melphalan SUN are considered sufficient and no additional risk minimisation measures are proposed by Sun Pharma for the safety concerns identified with melphalan.

### *VI.2.6 Planned post-authorization development plan*

None.

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

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| 1.0 | 17-Mar-17 | *Important identified risks*<br>• Hypersensitivity reactions<br>• Myelosupression<br>• Tumour lysis syndrome<br>• Malignancy<br>• Injection site reactions<br>*Important potential risks*<br>• Infections<br>• Gastrointestinal toxicities including haemorrhagic enterocolitis when used in combination with Nalidixic acid | New RMP issue for new NL/DCP. |

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| | | • Decreased clearance in patients with renal impairment<br>• Mutagenicity<br>*Missing information*<br>• Use in elderly patients<br>• Use during pregnancy and breastfeeding | |
| 1.1 (current) | 25-Oct-2017 | *Important identified risks*<br>• Mutagenicity<br>• Myelosupression<br>• Tumour lysis syndrome<br>• Malignancy<br>*Important potential risks*<br>• Gastrointestinal toxicities including haemorrhagic enterocolitis when used in combination with Nalidixic acid<br>• Decreased clearance in patients with renal impairment<br>*Missing information*<br>• Use in elderly patients | Following day 70 Preliminary Assessment Report of RMS, NL (Procedure no: NL/H/3954/001/DC) the summary of safety concerns was updated as following:<br>-Some important risks have been deleted:<br>• two Important identified risks "Hypersensitivity reactions" and "Injection side reactions"<br>• One Important potential risk "Infections"<br>One Important potential risk has been reconsidered as Important identified risk "Mutagenicity"<br>Missing information "Use during pregnancy and breastfeeding" has been deleted.<br>Part III, Part V and Part VI were also amended in line with changes performed in the summary of safety concerns.<br>Annex 2 was updated with revised SmPC and PL. |