PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion:

This is a summary of the risk management plan (RMP) for Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion. The RMP details important risks of Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion, how these risks can be minimised, and how more information will be obtained about Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion's risks and uncertainties (missing information).

Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion's summary of product characteristics (SmPC) and package leaflet (PL) give essential information to healthcare professionals and patients on how Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion should be used.

Important new concerns or changes to the current ones will be included in updates of Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion's RMP.

I. The medicine and what it is used for

Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion is authorised to treat cancer. It is used for:

- Multiple myeloma – a type of cancer that develops from cells in the bone marrow called plasma cells (that 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.

Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion contains melphalan hydrochloride as the active substance and it is given by parenteral route.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion, together with measures to minimise such risks and the proposed studies for learning more about Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size- the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status- the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Cancer (malignancy) • Ability of an agent to cause damage to the DNA (Mutagenicity) • Abnormal release of large quantities of cellular components into the blood following rapid death of cancer cells (Tumour lysis syndrome)
Important potential risks	• Harmful effects on digestive tract including bleeding due to inflammation of the lining of the intestine when used simultaneously with nalidixic acid (a medicine used for urine infections) (Gastrointestinal toxicities including haemorrhagic enterocolitis when used in combination with Nalidixic acid) • Decreased elimination of this medicine in patients with kidney problems (Decreased clearance in patients with renal impairment)
Missing information	• Use in older people (use in elderly patients)

II.B Summary of important risks

Important identified risks

Cancer (Malignancy)	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that melphalan has been reported to be leukaemogenic (promotes blood cancer). There have been reports of acute leukaemia (blood cancer) occurring after melphalan treatment for diseases such as amyloid, malignant melanoma (cancer of nervous system), multiple myeloma (cancer that develops from cells in the bone marrow called plasma cells), macroglobulinaemia, cold agglutinin syndrome (auto-immune disease) and ovarian cancer.
Risk factors and risk groups	The risk factors for secondary malignancies are as follows: • Shared Environmental Risk Factors: Lifestyle factors, such as smoking, alcohol, exercise, sun exposure, and diet, human papilloma virus infection. • Genetic Risk Factors: eg. Retinoblastoma (cancer of light detecting tissue of eye), mutations in the genes BRCA1 and BRCA2. • Therapy-Related Secondary Cancers: Radiation therapy and chemotherapy used to treat a primary cancer
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4 and 4.8 • PIL section 4 • Proposed pack size: Each pack contains 1 vial with powder (50 mg melphalan) and 1 vial with solvent (10 ml) • Medicinal product subject to restricted medical prescription (under the supervision of a specialist doctor who is experienced in management of malignant disease) **Additional risk minimisation measures:** • No risk minimisation measures
Ability of an agent to cause damage to the DNA (Mutagenicity)	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that, melphalan is mutagenic in animals and chromosome aberrations have been observed in patients being treated with the drug.
Risk factors and risk groups	Possible risk factors that can induce mutagenicity includes: • Chemical agents including alkylating agents, metal ions etc. • Physical agents like radiation therapy. • Biological agents like virus, bacteria.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.6 and 5.3

	• Recommendation for not using Melphalan during pregnancy and breast-feeding unless clinical condition of woman requires treatment is mentioned in SmPC section 4.6. • Proposed pack size: Each pack contains 1 vial with powder (50 mg melphalan) and 1 vial with solvent (10 ml) • Medicinal product subject to restricted medical prescription (under the supervision of a specialist doctor who is experienced in management of malignant disease) **Additional risk minimisation measures:** • No risk minimisation measures

Abnormal release of large quantities of cellular components into the blood following rapid death of cancer cells (Tumour lysis syndrome)	
Evidence for linking the risk to the medicine	Published literature and SmPC mentions that, tumour lysis syndrome is associated with all high dose chemotherapy including melphalan.
Risk factors and risk groups	Certain patient factors such as advanced age and the presence of pre-existent renal and cardiac diseases are well-established risk factor for tumour lysis syndrome. In addition, a baseline increase in serum uric acid, phosphorus, potassium, and lactate dehydrogenase (LDH) also portends a greater risk of this condition.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4 • Proposed pack size: Each pack contains 1 vial with powder (50 mg melphalan) and 1 vial with solvent (10 ml) • Medicinal product subject to restricted medical prescription (under the supervision of a specialist doctor who is experienced in management of malignant disease) **Additional risk minimisation measures:** • No risk minimisation measures

Important potential risks

Harmful effects on digestive tract including bleeding due to inflammation of the lining of the intestine when used simultaneously with nalidixic acid (a medicine used for urine infections) [Gastrointestinal toxicities including haemorrhagic enterocolitis when used in combination with Nalidixic acid]

Evidence for linking the risk to the medicine	Published literature and SmPC mentions that, the incidence of diarrhoea, vomiting and stomatitis becomes the dose-limiting toxicity in patients given high intravenous doses of melphalan in association with autologous bone marrow transplantation. Nalidixic acid together with high-dose intravenous melphalan has caused deaths in children due to haemorrhagic enterocolitis.
Risk factors and risk groups	Risk factors for chemotherapy induced oral mucositis: Treatment-related • Type of medication • Dose • Schedule of medication (e.g. number of cycles) • Route of administration • Concomitant radiation therapy • Dose and field of radiation Patient-related • Type of malignancy • Age • Poor oral health and hygiene • Salivary gland dysfunction • Body mass index • Gender • Genetic polymorphisms in drug metabolizing enzymes and Tumor necrosis factor-alpha (TNF-α) • Co-morbid disease states (e.g. psoriasis, Addison's disease, diabetes) Incidence and severity of CINV are affected by patient specific and treatment specific factors. Characteristics associated with a higher risk include: • Female sex • Age greater than 3 years • Anxiety • Motion sickness • Poor control with previous chemotherapy Treatment related risk factors include: • Emetic potential • Schedule • Dose

	• Route • Rate of drug administration As per the SmPC, risk factor for melphalan induced haemorrhagic enterocolitis include: • Concomitant use of nalidixic acid
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.5 and 4.8 • PIL sections 2 and 4 • Proposed pack size: Each pack contains 1 vial with powder (50 mg melphalan) and 1 vial with solvent (10 ml) • Medicinal product subject to restricted medical prescription (under the supervision of a specialist doctor who is experienced in management of malignant disease) **Additional risk minimisation measures:** • No risk minimisation measures

Decreased elimination of this medicine in patients with kidney problems (Decreased clearance in patients with renal impairment)	
Evidence for linking the risk to the medicine	SmPC mentions that, melphalan clearance may be reduced in patients with renal impairment who may also have uraemic marrow suppression.
Risk factors and risk groups	Patients with renal impairment
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.4, 4.8 and 5.2 • PIL sections 2, 3 and 4 • Recommendation to use a reduced dosage initially until tolerance is established, is included in SmPC section 4.2. • Proposed pack size: Each pack contains 1 vial with powder (50 mg melphalan) and 1 vial with solvent (10 ml) • Medicinal product subject to restricted medical prescription (under the supervision of a specialist doctor who is experienced in management of malignant disease) **Additional risk minimisation measures:** • No risk minimisation measures

Missing information

Use in older people (use in elderly patients)	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.2 • PIL section 3 • Proposed pack size: Each pack contains 1 vial with powder (50 mg melphalan) and 1 vial with solvent (10 ml) • Medicinal product subject to restricted medical prescription (under the supervision of a specialist doctor who is experienced in management of malignant disease) **Additional risk minimisation measures:** • No risk minimisation measures

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Melphalan Pharmexon 50 mg powder and solvent for solution for injection/infusion.