Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Melphalan Tillomed 50 mg powder and solvent for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains melphalan hydrochloride equivalent to 50 mg melphalan.
Each vial of solvent contains 10 ml of solvent.
After reconstitution, each ml of the reconstituted solution contains 5 mg melphalan.

Excipient(s) with known effect:
After reconstitution each vial contains 53.5 mg sodium, 0.4 g ethanol and 6.2 g propylene glycol.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion
Powder: White to pale yellow lyophilized powder
Solvent: A clear colourless solution, free from visible particles
pH of the reconstituted solution is between 6.0 and 7.0

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Melphalan, at conventional intravenous dose, is indicated in the treatment of multiple myeloma and advanced ovarian cancer.
2. Melphalan, at high intravenous dose, is indicated, with or without haematopoietic stem cell transplantation, for the treatment of multiple myeloma and childhood neuroblastoma.
3. Melphalan, administered by regional arterial perfusion, is indicated in the treatment of localised malignant melanoma of the extremities and localised soft tissue sarcoma of the extremities.

4.2 Posology and method of administration

Treatment with melphalan should be supervised by a physician experienced in the use of anticancer therapies.

General information
Melphalan is for intravenous use and regional arterial perfusion only. Melphalan should not be given without haematopoietic stem cell rescue at doses of above 140 mg/m^2.

For intravenous administration, it is recommended that melphalan is injected slowly into a fast-running infusion solution via a swabbed injection port. If direct injection into a fast-running infusion is not appropriate, melphalan may be administered diluted in an infusion bag.
Care should be taken to avoid possible extravasation of melphalan and in cases of poor peripheral venous access, consideration should be given to use of a central venous line.
If high dose melphalan is administered with or without autologous bone marrow transplantation, administration via a central venous line is recommended. In view of the hazards involved and the level of supportive care required (see section 4.4), the administration of high dose melphalan should be confined to specialist centres, with the appropriate facilities and only be conducted by experienced clinicians.
For regional arterial perfusion, the literature should be consulted for detailed methodology.
Protect the patient during intravenous administration against external contact with the melphalan solution for injection/infusion (see section 4.4).

Thromboembolic events

Thromboprophylaxis should be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors (see sections 4.4 and 4.8).
If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone may be restarted at the original dose dependent upon a benefit-risk assessment. The patient should continue anticoagulation therapy during the course of melphalan treatment.

Posology

Multiple myeloma
Conventional dose
Melphalan is administered on an intermittent basis alone, or in combination with other cytotoxic drugs. Administration of prednisone has also been included in a number of regimens.
When used as a single agent, a typical intravenous melphalan dose schedule is 0.4 mg/kg body weight (16 mg/m^2 body surface area) repeated at appropriate intervals (e.g. once every 4 weeks), provided there has been recovery of the peripheral blood count during this period.

High dose
High-dose regimens generally employ single intravenous doses of between 100 and 200 mg/m^2 body surface area (approximately 2.5 to 5.0 mg/kg body weight), but haematopoietic stem cell rescue becomes essential following doses in excess of 140 mg/m^2 body surface area.

Ovarian adenocarcinoma
When used intravenously as a single agent, a dose of 1 mg/kg body weight (approximately 40 mg/m^2 body surface area) given at intervals of 4 weeks has often been used.
When combined with other cytotoxic drugs, intravenous doses of between 0.3 and 0.4 mg/kg body weight (12 to 16 mg/m^2body surface area) have been used at intervals of 4 to 6 weeks.
Advanced neuroblastoma
Doses of between 100 and 240 mg/m^2 body surface area (sometimes divided equally over 3 consecutive days) together with haematopoietic stem cell rescue, have been used either alone or in combination with radiotherapy and/or other cytotoxic drugs.

Malignant melanoma
Hyperthermic regional perfusion with melphalan has been used as an adjuvant to surgery for early malignant melanoma and as palliative treatment for advanced but localised disease. The scientific literature should be consulted for details of perfusion technique and dosage used. A typical dose range for upper extremity perfusions is 0.6-1.0 mg/kg bodyweight and for lower extremity perfusions is 0.8-1.5 mg/kg body weight.

Soft tissue sarcoma
Hyperthermic regional perfusion with melphalan has been used in the management of all stages of localised soft tissue sarcoma, usually in combination with surgery. The scientific literature should be consulted for details of perfusion technique and dosage used. A typical dose range for upper extremity perfusions is 0.6-1.0 mg/kg body weight and for lower extremity perfusions is 1-1.4 mg/kg body weight.

Special populations
Paediatric population
Melphalan, at conventional dosage, is only rarely indicated in children and dosage guidelines cannot be stated.
High dose melphalan, in association with haematopoietic stem cell rescue, has been used in childhood neuroblastoma and dosage guidelines based on body surface area may be used.
Please refer also to the paragraph on Propylene glycol in section 4.4.

Elderly
Although melphalan is frequently used at conventional dose 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. Consideration should therefore be given to ensure adequate performance status and organ function, before using high dose melphalan in elderly patients.

Patients with impaired renal function

Melphalan clearance, though variable, may be decreased in renal impairment.

Currently available pharmacokinetic data do not justify an absolute recommendation on dosage reduction when administering melphalan to patients with renal impairment, but it may be prudent to use a reduced dosage initially until tolerance is established. When melphalan is used at conventional intravenous dosage (8-40 mg/m^2 body surface area), it is recommended that the initial dose should be reduced by 50% and subsequent dosage determined according to the degree of haematological suppression.

For high intravenous doses of melphalan (100 to 240 mg/m^2 body surface area), the need for dose reduction depends upon the degree of renal impairment, whether haematopoietic stem cells are re-infused, and therapeutic need. As a guide, for high dose melphalan treatment without haematopoietic stem cell rescue in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min) a dose reduction of 50% is usual.

High dose melphalan with haematopoietic stem cell rescue has been used successfully even in dialysis dependent patients with end-stage renal failure. The relevant literature should be consulted for details.

Please refer also to the paragraph on Propylene glycol in section 4.4.

Patients with impaired hepatic function

Please refer to the paragraph on Propylene glycol in section 4.4.

Method of Administration

Injection/infusion

For instructions on reconstitution, and if applicable dilution, of the medicinal product before administration, see section 6.6.

After reconstitution the appearance of the medicinal product should be a clear solution, see section 6.6.

4.3 Contraindications

1. Hypersensitivity to the active substance or any of the excipients listed in section 6.1
2. Breastfeeding (see section 4.6)

4.4 Special warnings and precautions for use

Melphalan is a cytotoxic drug, which falls into the general class of alkylating agents. It should be prescribed only by physicians experienced in the management of malignant disease with such agents. As with all high dose chemotherapy, precautions should be taken to prevent tumour lysis syndrome.

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.

The eyes, skin and the mucous membranes of patients need to be protected against contact with the melphalan solution for injection/infusion or reconstituted solution.

Since melphalan is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be delayed or adjusted if necessary.

Melphalan can cause local tissue damage, should extravasation occur and consequently, it should not be administered by direct injection into a peripheral vein.

In patients receiving high dose melphalan , consideration should be given to the prophylactic administration of anti-infective agents and the administration of blood products as required. Consideration should be given to ensure adequate performance status and organ function before using high dose melphalan.

Melphalan should be used with caution in patients who have undergone recent radiotherapy or chemotherapy in view of increased bone marrow toxicity.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be practiced when either partner is receiving melphalan up to three months after end of treatment. For ovarian cancer, non-hormonal contraceptive methods are advised.

Monitoring

Since melphalan is a potent myelosuppressive agent, it is essential that careful attention should be paid to the monitoring of blood counts, to avoid the possibility of excessive myelosuppression and the risk of irreversible bone marrow aplasia. Blood counts may continue to fall after treatment is stopped, so at the first sign of an abnormally large fall in leukocyte or platelet counts, treatment should be temporarily interrupted.

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. Cyclophosphamide pretreatment appears to reduce the severity of gastro-intestinal damage induced by high-dose melphalan and the literature should be consulted for details.

Renal Impairment
Melphalan clearance may be reduced in patients with renal impairment who may also have uraemic marrow suppression. Dose reduction may therefore be necessary (see Section 4.2). See section 4.8 for elevation of blood urea. Patients with renal impairment should be closely monitored for signs/signals of overdose.

Thromboembolic events
Patients treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone, have an increased risk of thromboembolic events (see section 4.8). Especially in patients with additional thrombotic risk factors antithrombotic prophylactic measures should be considered (see sections 4.2 and 4.8).

Mutagenicity
Melphalan is mutagenic in animals and chromosome aberrations have been observed in patients being treated with the drug.

Carcinogenicity
Melphalan has been reported to be leukaemogenic. There have been reports of acute leukaemia occurring after melphalan treatment for diseases such as amyloid, malignant melanoma, multiple myeloma, macroglobulinaemia, cold agglutinin syndrome and ovarian cancer.

A comparison of patients with ovarian cancer who received alkylating agents with those who did not, showed that the use of alkylating agents, including melphalan, significantly increased the incidence of acute leukaemia.

The leukaemogenic risk must be balanced against the potential therapeutic benefit when considering the use of melphalan.

5% Ethanol (alcohol)
This medicinal product contains 5 % ethanol (alcohol), i.e. 0,4 g per vial.
Harmful for those suffering from alcoholism.
To be taken into account in pregnant women, children and high-risk groups such as patients with liver disease, or epilepsy.

Propylene glycol
This medicinal product contains propylene glycol which may cause alcohol-like symptoms.
Medical monitoring is required if used in patients with impaired renal or hepatic function.
Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.

Sodium
This medicinal product contains 53.5 mg sodium per vial, equivalent to 2.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Seven vials reflect the lowest number of vials for which the threshold of 17 mmol (391 mg) of sodium is reached/ exceeded.

4.5 Interaction with other medicinal products and other forms of interaction

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see section 4.4).
Nalidixic acid together with high-dose intravenous melphalan has caused deaths in children due to haemorrhagic enterocolitis. Combined treatment of melphalan with nalidixic acid should be avoided.
In the paediatric population, for the busulfan-melphalan regimen it has been reported that the administration of melphalan less than 24 hours after the last oral busulfan administration may influence the development of toxicities.
Impaired renal function has been described in bone marrow transplant patients who received intravenous melphalan and who subsequently received ciclosporin to prevent graft-versus-host disease.
Ethanol: please refer to the paragraph on Propylene glycol in section 4.4 above.

4.6 Fertility, pregnancy and lactation

Contraception for men and women of childbearing potential
As with all cytotoxic treatments, male and female patients who use melphalan should use effective and reliable contraceptive methods up until three months after cessation of treatment. The use of hormonal contraceptives should be avoided in ovarian cancer.

Pregnancy

There are no or limited amount of data from the use of melphalan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Risk for human is not known, but due to the mutagenic properties and structural similarity of melphalan with known teratogenic compounds, it is possible that melphalan can induce congenital malformations in offspring of treated patients. Melphalan should not be used during pregnancy unless the clinical condition of the woman requires treatment with melphalan.

Breast-feeding

It is unknown whether melphalan or its metabolites are excreted in human milk. Due to its mutagenic properties, melphalan is contraindicated during breastfeeding (see section 4.3).

Fertility

Melphalan causes suppression of ovary function in premenopausal women resulting in amenorrhoea in a large number of patients.

Studies in animals have shown melphalan can have adverse effects on spermatogenesis (see section 5.3). Therefore it is possible that melphalan may cause temporary or permanent adverse effects on male fertility. It is recommended that men who are receiving treatment with melphalan not father a child during treatment and up to 3 months afterwards. Cryopreservation of semen before treatment is advised.

4.7 Effects on ability to drive and use machines

There are no data regarding the effect of melphalan treatment on the ability to drive and use machines. Based on the pharmacological profile such an effect is not anticipated. When advising patients treated for malignant disease it is recommended to consider their general health status.

4.8 Undesirable effects

For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the indication and dose received and also when given in combination with other therapeutic agents.

The following convention has been utilised for the classification of frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare ≥ 1/10,000 to < 1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

MedDRA system organ class	**Frequency**	**Adverse reactions**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Not known	secondary acute myeloid leukaemia and myelodysplastic syndrome (see section 4.4)
Blood and lymphatic system disorders	Very common	bone marrow depression, leading to leukopenia, thrombocytopenia, neutropenia and anaemia.
	Rare	hemolytic anaemia
Immune system disorders	Rare	allergic reactions[1] (see skin and subcutaneous tissue disorders).
Respiratory, thoracic and mediastinal disorders	Rare	interstitial pneumonitis and pulmonary fibrosis (including fatal reports).
Gastrointestinal disorders	Very common	nausea, diarrhoea and vomiting, stomatitis at high dose.
	Rare	stomatitis at conventional dose.
Hepato-biliary disorders	Rare	hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice; veno-occlusive disease following high-dose therapy.
Skin and subcutaneous tissue disorders	Very common	alopecia at high dose.
	Common	alopecia at conventional dose
	Rare	maculopapular rashes and pruritus (see also immune system disorders).

Musculoskeletal and connective tissue disorders[2]	Very common	muscular atrophy, muscle fibrosis, myalgia, increase in creatinine phosphokinase in the blood.
	Common	compartment syndrome
	Not known	muscle necrosis, rhabdomyolysis.
Renal and urinary disorders	Common	blood urea increased[3]
Reproductive system and breast disorders	Not known	azoospermia and amenorrhoea
Vascular disorders[4]	Not known	deep vein thrombosis and pulmonary embolism
General disorders and administration site conditions	Very common	subjective and transient heat sensation of warmth and / or tingling

[1]Allergic reactions to melphalan such as urticaria, oedema, skin rashes and anaphylactic shock have been reported uncommonly following initial or subsequent dosing, particularly after intravenous administration. Cardiac arrest has also been reported rarely in association with such events
[2]Only with melphalan infusion after administration of regional perfusion in the limb
[3]Temporary significant elevation of the blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage
[4]The clinically important adverse reactions associated with the use of melphalan in combination with thalidomide and prednisone or dexamethasone and to a lesser extend melphalan with lenalidomide and prednisone include: deep vein thrombosis and pulmonary embolism (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms and signs
Gastro-intestinal effects, including nausea, vomiting and diarrhoea are the most likely signs of acute oral overdosage. The immediate effects of acute intravenous overdose are nausea and vomiting. Damage to the gastro-intestinal mucosa may also ensue and diarrhoea, sometimes haemorrhagic, has been reported after overdose. The principal toxic effect is bone marrow suppression, leading to leucopenia, thrombocytopenia and anaemia.

Treatment
General supportive measures, together with appropriate blood and platelet transfusions, should be instituted if necessary and consideration given to hospitalisation, antibiotic cover, the use of haematological growth factors.
There is no specific antidote. The blood picture should be closely monitored for at least four weeks following overdose until there is evidence of recovery.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, Antineoplastic agents. Alkylating agents. Nitrogen mustard analogues; ATC code: L01AA03

Mechanism of action
Melphalan is a bifunctional alkylating agent. Formation of carbonium intermediates from each of the two bis-2-chloroethyl groups enables alkylation through covalent binding with the 7-nitrogen of guanine on DNA, cross-linking the two DNA strands and thereby preventing cell replication

5.2 Pharmacokinetic properties

Absorption
The absorption of oral melphalan is highly variable with respect to both the time to first appearance of the drug in plasma and peak plasma concentration.
In studies of the absolute bioavailability of melphalan the mean absolute bioavailability ranged from 56 to 85%.
Intravenous administration can be used to avoid variability in absorption associated with myeloablative treatment.

Distribution

Melphalan is moderately bound to plasma proteins with reported percent binding ranging from 69% to 78%. There is evidence that the protein binding is linear in the range of plasma concentrations usually achieved in standard dose therapy, but that the binding may become concentration-dependent at the concentrations observed in high-dose therapy. Serum albumin is the major binding protein, accounting for about 55 to 60% the binding, and 20% is bound to α_1-acid glycoprotein. In addition, melphalan binding studies have revealed the existence of an irreversible component attributable to the alkylation reaction with plasma proteins.

Following administration of a two-minute infusion of doses ranging from 5 to 23 mg/m^2 body surface area (approximately 0.1 to 0.6 mg/kg bodyweight) to 10 patients with ovarian cancer or multiple myeloma, the mean volumes of distribution at steady state and central compartment were 29.1 ± 13.6 litres and 12.2 ± 6.5 litres, respectively.

In 28 patients with various malignancies who were given doses of between 70 and 200 mg/m^2 body surface area as a 2- to 20-min infusion, the mean volumes of distribution at steady state and central compartment were, respectively, 40.2 ± 18.3 litres and 18.2 ± 11.7 litres.

Following hyperthermic (39°C) perfusion of the lower limb with 1.75 mg/kg bodyweight, mean volumes of distribution at steady state and central compartment of 2.87 ± 0.8 litres and 1.01 ± 0.28 litres, respectively, were recorded in 11 patients with advanced malignant melanoma.

Melphalan displays limited penetration of the blood-brain barrier. Several investigators have sampled cerebrospinal fluid and found no measurable drug. Low concentrations (~10% of that in plasma) were observed in a single high-dose study in children.

Biotransformation

In vivo and *in vitro* data suggest that spontaneous degradation rather than enzymatic metabolism is the major determinant of the drug's half-life in man.

The metabolites monohydroxy melphalan and dihydroxy melphalan have been detected in plasma, with peak levels after 60 minutes and 105 minutes, respectively.

Elimination

In 13 patients given oral melphalan at 0.6 mg/kg bodyweight, the plasma mean terminal elimination half-life was 90 ± 57 min with 11% of the drug being recovered in the urine over 24 h.

In 8 patients given a single bolus dose of 0.5 to 0.6 mg/kg bodyweight, the composite initial and terminal half-lives were reported to be 7.7 ± 3.3 min and 108 ± 20.8 min, respectively. Following administration of a two-minute infusion of doses ranging from 5 to 23 mg/m^2 body surface area (approximately 0.1 to 0.6 mg/kg bodyweight) to 10 patients with ovarian cancer or multiple myeloma, the pooled initial and terminal half-lives were, respectively, 8.1 ± 6.6 min and 76.9 ± 40.7 min. A mean clearance of 342.7 ± 96.8 ml/min was recorded.

In 15 children and 11 adults given high-dose intravenous melphalan (140 mg/m^2 body surface area) with forced diuresis, the mean initial and terminal half-lives were found to be 6.5 ± 3.6 min and 41.4 ± 16.5 min, respectively. Mean initial and terminal half-lives of 8.8 ± 6.6 min and 73.1 ± 45.9 min, respectively, were recorded in 28 patients with various malignancies who were given doses of between 70 and 200 mg/m^2 body surface area as a 2- to 20-min infusion. The mean clearance was 581.5 ± 182.9 ml/min.

Following hyperthermic (39°C) perfusion of the lower limb with 1.75 mg/kg bodyweight, mean initial and terminal half-lives of 3.6 ± 1.5 min and 46.5 ± 17.2 min, respectively, were recorded in 11 patients with advanced malignant melanoma. A mean clearance of 55.0 ± 9.4 ml/min was recorded.

Special patient populations

Renal impairment

Melphalan clearance may be decreased in renal impairment (see section 4.2 and 4.4)

Elderly

No correlation has been shown between age and melphalan clearance or with melphalan terminal elimination half-life (see section 4.2)

5.3 Preclinical safety data

Mutagenicity

Melphalan is a cytostatic agent and mutagenicity has therefore not been thoroughly investigated in pre-clinical studies. Melphalan was mutagenic *in vivo* causing chromosomal aberrations. Clinical information on potential toxicity of melphalan is provided in sections 4.4 and 4.6.

Reproductive toxicity and fertility

Melphalan was teratogenic in rat after single dose exposure in reproductive toxicity studies. In repeated dose reproductive toxicity studies, melphalan was maternal toxic and induced congenital malformations, intra-uterine death, growth retardation and disrupted development.
A single dose of melphalan in male mice induced cytotoxicity and chromosomal aberrations in sperm cells. In female mice a reduction in number of pups per litter was observed. After recovery the number of pups per litter was also reduced over time, which was related to a reduced number of follicles.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Povidone
Hydrochloric acid, dilute (for pH adjustment)

Solvent
Sodium citrate dihydrate
Propylene glycol
Ethanol
Water for injections

6.2 Incompatibilities

Melphalan is not compatible with infusion solutions containing dextrose and it is recommended that ONLY sodium chloride 9 mg/ml (0.9%) solution for injection is used.

6.3 Shelf life

Unopened powder and solvent: 2 years
Reconstituted Solution: Once reconstituted the product should be used immediately. Any unused portion should be discarded. Melphalan has a limited shelf-life and the rate of decomposition increases rapidly as the temperature increases.
Reconstituted and further diluted solution for infusion: The maximum time from the start of reconstitution to the end of infusion should not exceed 1.5 hours at room temperature (approximately 25°C).

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the vial in the outer carton, in order to protect from light. For storage conditions of the medicinal product after reconstitution and dilution, see section 6.3.

6.5 Nature and contents of container

Powder: Clear type I glass vial sealed with fluorinated polymer coated bromobutyl rubber stopper and flip off aluminium seal having orange colour polypropylene button. Vials may or may not be sleeved with shrink sleeves.

Pack size: 1 vial containing 50 mg melphalan
Solvent: Clear type I glass vial sealed with fluorinated polymer coated bromobutyl rubber stopper and flip off aluminium seal having orange colour polypropylene button.

Pack size: 1 vial containing 10 ml
Each pack contains 1 vial with powder and 1 vial with solvent.

6.6 Special precautions for disposal and other handling

Procedures for proper handling and disposal of cytotoxic medicinal products should be observed:
1.The employees are to be instructed in the reconstitution of the drug.
2.Pregnant women should be excluded from handling this medicine.
3.The personnel should wear suitable protective clothing with face masks, safety goggles and gloves when reconstituting the preparation.

4.Any items used for administration or cleaning, including gloves, should be disposed of in waste containers for contaminated material to high-temperature combustion. Liquid waste can be discharged with plenty of water.

In case of accidental eye contact with Melphalan immediately rinse with sodium chloride eyewash or plenty of water and immediately consult a doctor. In case of skin contact, immediately wash the affected areas with soap and plenty of cold water and consult a doctor immediately. The spilled solution should be immediately wiped with a damp paper towel, which must then be disposed of safely. The contaminated surfaces must be washed with plenty of water.

Reconstitution
Melphalan should be prepared at room temperature (approximately 25°C), by reconstituting the powder with the solvent-diluent provided.
It is important that both the powder and the solvent provided are at room temperature (approximately 25°C) before starting reconstitution.
10 ml of the solvent should be added quickly as a single quantity into the vial containing the powder, using a sterile needle and syringe. A 21 gauge or higher gauge needle should be used for piercing of vial stopper during reconstitution. For smooth and effective penetration, the needle should be inserted perpendicularly into the stopper, not too fast or too rough without twisting. . Immediately shake the vial vigorously (for approximately 5 minutes) until a clear solution, without visible particles, is obtained. Rapid addition of diluent followed by immediate vigorous shaking is important for proper dissolution.
Shaking of the formulation leads to a significant amount of very small air bubbles. These bubbles can remain for 2 to 3 minutes as the resulting solution is quite viscous. This can make it difficult to assess the clarity of the solution.
Each vial must be reconstituted individually in this manner. The resulting solution contains the equivalent of 5 mg per ml anhydrous melphalan. Failure to follow above mentioned preparation steps may result in incomplete dissolution of Melphalan.
Melphalan solution has limited stability and should be prepared immediately before use.
The reconstituted solution should not be refrigerated as this will cause precipitation.

Admixture
Take 10 ml of above reconstituted solution having concentration of 5 mg/ml of anhydrous melphalan into infusion bag containing 100 ml of 0.9% Sodium chloride injection. Mix this diluted solution thoroughly to give nominal concentration of 0.45 mg/ml of anhydrous melphalan.
When further diluted in an infusion solution, Melphalan has reduced stability and the rate of degradation increases rapidly with rise in temperature. **If Melphalan is infused at a room temperature of approximately 25°C, the maximum time from preparation of the solution to the completion of infusion should not exceed 1.5 hours.**
Melphalan is not compatible with infusion solutions containing dextrose and it is recommended that only sodium chloride 9 mg/ml (0.9%) solution for injection is used.
Should any visible turbidity or crystallisation appear in the reconstituted or diluted solutions, the preparation must be discarded.

Disposal
Any solution unused after 1.5 hours should be discarded according to standard guidelines for handling and disposal of cytotoxic medicinal products.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic medicinal products.

7 MARKETING AUTHORISATION HOLDER

Tillomed Pharma GmbH
Mittelstrasse 5/5a
Schonefeld
12529
Germany

8 MARKETING AUTHORISATION NUMBER

PA22720/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation: 19th August 2019

Date of last renewal: 13th March 2024

10 DATE OF REVISION OF THE TEXT

November 2023