Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Melphalan medac is supplied as a unit pack comprising of a vial of powder containing melphalan hydrochloride equivalent to 50 mg melphalan, and a vial of solvent containing 10 ml of solvent.

Where a pack is reconstituted with 10 ml of the solvent, the resultant solution contains 5 mg/ml anhydrous melphalan.

Excipients with known effect
Each vial of solvent contains 53 mg of sodium as Sodium citrate, 0.52 ml (0.4 g) of ethanol and 6.0 ml of propylene glycol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion

Powder: A off-white to light brown freeze-dried powder.
Solvent: A clear, colourless solution, free from visible particles.

The pH of the reconstituted solution is 6.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Melphalan medac, at conventional intravenous dosage, is indicated in the treatment of multiple myeloma and advanced ovarian cancer.

Melphalan medac, at high intravenous dosage, is indicated, with or without haematopoietic stem cell transplantation, for the treatment of multiple myeloma and childhood neuroblastoma.

Melphalan medac, 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.

In the above indications, Melphalan medac may be used alone or in combination with other cytotoxic drugs.

4.2 Posology and method of administration

Melphalan medac should only be prescribed for patients by a specialist doctor who is experienced in management of malignant disease. As Melphalan medac is a myelosuppressive agent, it is necessary to perform blood count test during therapy. If necessary, discontinue administration or adjust dose.
The use of Melphalan medac should only be performed with careful haematological control. If the leukocyte or platelet count drops unusually, the treatment should be temporarily interrupted (see section 4.4).

Posology

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

Multiple myeloma

Melphalan medac 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 dosage 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 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. Hydration and forced diuresis are also recommended.

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^2 body 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. 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.

Paediatric population
Melphalan at conventional dosage is only rarely indicated in children and dosage guidelines cannot be stated. High dose melphalan injection, in association with haematopoietic stem cell rescue, has been used in childhood neuroblastoma and dosage guidelines based on body surface area, as for adults, may be used.

Elderly
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. Consideration should therefore be given to ensure adequate performance status and organ function, before using high-dose Melphalan medac in elderly patients.

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

When Melphalan medac is used at conventional intravenous dosage (16 to 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. Melphalan medac should not be given without haematopoietic stem cell rescue at doses of above 140 mg/m^2.

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 (above 140 mg/m^2) without haematopoietic stem cell rescue should not be used in patients with more severe renal impairment.

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.

Thromboembolic events
Melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism).

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.

Method of administration

For intravenous administration, it is recommended that Melphalan medac 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 medac may be administered diluted in an infusion bag.

Melphalan medac is not compatible with infusion solutions containing dextrose and it is recommended that only sodium chloride intravenous infusion 0.9 % w/v is used.

For instructions on dilution before administration, see section 6.6.

When further diluted in an infusion solution, Melphalan medac has reduced stability and the rate of degradation increases rapidly with rise in temperature. If Melphalan medac is infused at a room temperature of approximately 25 °C, the total time from preparation of the injection solution to the completion of infusion should not exceed 1.5 hours.

Should any visible turbidity or crystallisation appear in the reconstituted or diluted solutions, the preparation must be discarded.

Care should be taken to avoid possible extravasation of Melphalan medac and in cases of poor peripheral venous access, consideration should be given to use of a central venous line.

If high dose Melphalan medac is administered with or without autologous bone marrow transplantation, administration via a central venous line is recommended.

Protect the patient during intravenous administration against external contact with the melphalan solution for injection/infusion (see section 4.4).

For regional arterial perfusion, the literature should be consulted for detailed methodology.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Lactation (see section 4.6)

4.4 Special warnings and precautions for use

Melphalan medac 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.

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

Melphalan medac solution can cause local tissue damage should extravasation occur, and consequently it should not be administered by direct injection into a peripheral vein. It is recommended that Melphalan medac solution is administered by injecting slowly into a fast-running intravenous infusion via a swabbed injection port, or via a central venous line.

In view of the hazards involved and the level of supportive care required, the administration of high dose melphalan should be confined to specialist centres, with the appropriate facilities and only be conducted by experienced clinicians.

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 not be given without haematopoietic stem cell rescue at doses of above 140 mg/m^2.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be practised when either partner is receiving Melphalan medac.

Safe handling of Melphalan medac

The handling of Melphalan medac formulations should follow guidelines for the handling of cytotoxic drugs. 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.

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

Neutropenia and thrombocytopenia

Increased rate of haematological toxicities, particularly, neutropenia and thrombocytopenia, was observed in elderly patients newly diagnosed with multiple myeloma, treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone. Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving combination drug regimens described (section 4.8).

Venous thromboembolic events

Patients treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone, have an increased risk of deep vein thrombosis and pulmonary embolism (see section 4.8). The risk appears to be greatest during the first 5 months of therapy, especially in patients with additional thrombotic risk factors (e.g. smoking, hypertension, hyperlipidaemia and history of thrombosis). These patients should be closely monitored and actions to minimize all modifiable risk factors should be undertaken. Thromboprophylaxis and dosing/anticoagulation therapy recommendations are provided in section 4.2. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. If a patient experiences any thromboembolic events, discontinue the treatment immediately and initiate the standard anticoagulation therapy. 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 throughout the course of treatment.

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.

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

Carcinogenicity (Second primary malignancy)
Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)
Melphalan, in common with other alkylating agents, has been reported to be leukaemogenic. There have been reports of acute leukaemia occurring after melphalan treatment for diseases such as amyloidosis, 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, especially if the use of melphalan in combination with thalidomide or lenalidomide and prednisone is considered, as it has been shown that these combinations may increase the leukaemogenic risk. Before, during and after treatment doctors must therefore examine the patient at all times by usual measurements to ensure the early detection of cancer and initiate treatment if necessary.

Solid tumours
Use of alkylating agents has been linked with the development of second primary malignancy (SPM). In particular, melphalan in combination with lenalidomide and prednisone and, to a lesser extent, thalidomide and prednisone has been associated with the increased risk of solid SPM in elderly newly diagnosed multiple myeloma patients.

Patient characteristics (e.g. age, ethnicity), primary indication and treatment modalities (e.g. radiation therapy, transplantation), as well as environmental risk factors (e.g. tobacco use) should be evaluated prior to melphalan administration.

Contraception
Due to an increased risk of venous thromboembolism in patients undergoing treatment with melphalan in combination with lenalidomide and prednisone or in combination with thalidomide and prednisone or dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception, she should switch to other reliable contraceptive methods (i.e. ovulation inhibitory progesterone-only pills such as desogestrel, barrier method, etc). The risk of venous thromboembolism continues for 4-6 weeks after discontinuing combined oral contraception.

Effects on fertility
Melphalan causes suppression of ovarian function in premenopausal women resulting in amenorrhoea in a significant number of patients.

There is evidence from some animal studies that melphalan can have an adverse effect on spermatogenesis. Therefore, it is possible that melphalan may cause temporary or permanent sterility in male patients.

Excipients with known effects
Sodium
This medicinal product contains 53 mg sodium per vial of solvent, equivalent to 2.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Ethanol
A dose of 240 mg/m^2 of this medicinal product administered to an adult weighing 70 kg would result in exposure to 47 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 7.8 mg/100 ml.
A dose of 240 mg/m^2 of this medicinal product administered to a newborn (child 0 year of age) and weighing 3 kg would result in exposure to 135 mg/kg of ethanol which may cause a rise in BAC of about 23 mg/100 ml, while to a child with 6 years of age and weighing 20 kg would result in exposure to 76 mg/kg of ethanol causing a rise in BAC of about 13 mg/100 ml.
For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml.
Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity.

Harmful for those suffering from alcoholism. To be taken into account in pregnant women and children, especially in children with liver disease or epilepsy.

Propylene glycol
This medicinal product contains 6.00 ml (6,240 mg) propylene glycol per vial of solvent.
While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus. As a consequence, administration of propylene glycol to pregnant patients should be considered on a case by case basis.
Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.
Various adverse events, such as hyperosmolality, lactic acidosis, renal dysfunction (acute tubular necrosis), acute renal failure, cardiotoxicity (arrhythmia, hypotension), central nervous system disorders (depression, coma, seizures), respiratory depression, dyspnoea, liver dysfunction, haemolytic reaction (intravascular haemolysis) and haemoglobinuria, or multisystem organ dysfunction, have been reported with high doses or prolonged use of propylene glycol. Therefore doses higher than 500 mg/kg/day may be administered in children but will have to be considered case by case.
Adverse events usually reverse following weaning off of propylene glycol, and in more severe cases following haemodialysis. Medical monitoring is required.

4.5 Interaction with other medicinal products and other forms of interactions

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.

In 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 were received high-dose intravenous melphalan and who subsequently received cyclosporin to prevent graft-versus-host disease.

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 six months after cessation of treatment.

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 cause congenital malformations in the offspring of treated patients.

The use of melphalan should be avoided whenever possible during pregnancy, particularly during the first trimester. In any individual case, the potential hazard to the foetus must be balanced against the expected benefit to the mother.

Breast-feeding
It is unknown whether melphalan or its metabolites are excreted in human milk.
Mothers receiving melphalan should not breast-feed.

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

There is evidence from some animal studies that melphalan can have an adverse effect on spermatogenesis (see section 5.3). Therefore, it is possible that melphalan may cause temporary or permanent sterility in male patients.

It is recommended that men who are receiving treatment with melphalan do not father a child during treatment and up to 6 months afterwards and that they have a consultation on sperm preservation before treatment due to the possibility of irreversible infertility as a result of melphalan treatment.

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).

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Not known: secondary acute myeloid leukaemia and myelodysplastic syndrome (see section 4.4), second primary malignancy (see section 4.4)

Blood and lymphatic system disorders
Very common: bone marrow depression leading to leukopenia, thrombocytopenia, neutropenia and anaemia
Rare: haemolytic anaemia
Increased rate of haematological toxicities, particularly, neutropenia and thrombocytopenia, was observed in elderly patients newly diagnosed with multiple myeloma treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone (see sections 4.4)

Immune system disorders
Rare: allergic reactions (see Skin and subcutaneous tissue disorders)
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.

Vascular disorders
Not known: deep vein thrombosis and pulmonary embolism
Deep vein thrombosis and pulmonary embolism have been associated with the use of melphalan in combination with thalidomide and prednisone or dexamethasone and to a lesser extend melphalan with lenalidomide and prednisone (see section 4.2 and 4.4).

Respiratory, thoracic and mediastinal disorders
Rare: interstitial pneumonitis and pulmonary fibrosis (including fatal reports)

Gastrointestinal disorders
Very common: nausea, vomiting and diarrhoea; stomatitis at high dose
Rare: stomatitis at conventional dose
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 pre-treatment appears to reduce the severity of gastro-intestinal damage induced by high-dose melphalan and the literature should be consulted for details.

Hepatobiliary disorders
Rare: hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice; veno-occlusive disease following high dose treatment

Skin and subcutaneous tissue disorders

Very common: alopecia at high dose
Common: alopecia at conventional dose
Rare: maculopapular rashes and pruritus (see Immune system disorders)

Musculoskeletal and connective tissue disorders
Injection, following isolated limb perfusion:
Very common: muscle atrophy, muscle fibrosis, myalgia, blood creatine phosphokinase increased
Common: compartment syndrome
Not known: muscle necrosis, rhabdomyolysis

Renal and urinary disorders
Common: temporary significant elevation of the blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage.

Reproductive system and breast disorders
Not known: azoospermia, amenorrhoea

General disorders and administration site conditions
Very common: subjective and transient sensation of warmth and/or tingling; pyrexia

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, Website: www.hpra.ie.

4.9 Overdose

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

General supportive measures, together with appropriate blood and platelet transfusions, should be instituted if necessary, and consideration given to hospitalisation, antibiotic cover and the use of haematological growth factors.

There is no specific antidote. The blood picture should be closely monitored for at least four weeks following overdosage until there is evidence of recovery.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, alkylating agents, nitrogen mustard analogues, ATC code: L01AA03.

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, crosslinking 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 α1-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/m² 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/m² 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.

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.

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 injection of melphalan, monohydroxymelphalan and dihydroxymelphalan were detected in the patients' plasma, reaching peak levels at approximately 60 min and 105 min, respectively. A similar half-life of 126 ± 6 min was seen when melphalan was added to the patients' serum in vitro (37 °C), suggesting that spontaneous degradation rather than enzymic metabolism may be the major determinant of the drug's half-life in man.

Following administration of a two-minute infusion of doses ranging from 5 to 23 mg/m² 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 i.v. melphalan (140 mg/m² 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/m² body surface area as a 2- to 20-min infusion. The mean clearance was 564.6 ± 159.1 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 mutagenic in animals.

Reproductive toxicity
Reproduction studies in rats using a single intraperitoneal injection of melphalan at a dose of 0.48 times the Maximum Recommended Human Dose (MRHD) revealed embryolethal and teratogenic effects. Congenital anomalies included those of the brain (underdevelopment, deformation, meningocele, and encephalocele), eye (anophthalmia and micropthalmos), reduction of the mandible and tail, and hepatocele. High foetal losses occurred and foetal abnormalities were observed after exposure to a minimum dose of 0.48 times the MRHD and 0.81 times the MRHD on Days 6 and 9, respectively. Single dose of 2.42 times the MRHD on Days 12 to 14 resulted in embryolethality (30 %) but not foetal abnormalities (see section 4.6).

Fertility studies
In mice, melphalan administered intraperitoneally at a dose of 7.5 mg/kg, showed reproductive effects attributable to cytotoxicity in specific male germ cell stages and induced dominant lethal mutations and heritable translocations in post-meiotic germ cells, particularly in mid to late stage spermatids.

Females received melphalan at clinically relevant exposure levels and were then housed with an untreated male for most of their reproductive life span. A pronounced reduction in litter size occurred within the first post-treatment interval, followed by an almost complete recovery. Thereafter, a gradual decline in litter size occurred. This was simultaneous with a reduction in the proportion of productive females, a finding associated with an induced reduction in the number of small follicles (see section 4.6).

Genotoxicity
Melphalan has been tested for genotoxicity in a number of short-term assays, both *in vitro* and *in vivo*.
In mice, intraperitoneal administration of melphalan at doses of 0.10-3.25 times the MRHD increased frequencies of dominant lethal mutations, chromosomal aberrations, sister chromatic exchange, micronuclei and DNA strand breaks.
The observed mutations originated primarily from large deletions in the postspermatogonial cells whereas other types of mutagenic mechanisms predominated in the spermatogonial cells.
This *in vivo* data is supported by in vitro studies showing that cell culture treatment with melphalan (at concentrations ranging from 0.1 to 25 microM) also induced DNA damage.
In addition, it induced aneuploidy and sex-linked recessive lethal mutations in Drosophila, and mutation in bacteria. It was positive with all strains in the Ames test at concentrations of 200 micrograms/plate and above. The mutagenic activity of melphalan was increased 3-fold in the presence of liver S9 metabolising preparations, which is unexpected since melphalan is not considered to need liver activation to produce a cytotoxic effect.

Carcinogenicity
Melphalan is a direct-acting alkylating agent that is carcinogenic via a genotoxic mechanism, which is sufficiently supported by animal studies.
Development of neoplastic tumours in rats was reported following intraperitoneal administration of melphalan at doses of 0.15-1.61 times the MRHD; in mice, the carcinogenic potential was observed at doses of 0.02-1.39 times the MRHD.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Freeze-dried powder
Povidone K-12
Hydrochloric acid (for pH adjustment)

Solvent
Sodium citrate anhydrous
Propylene glycol
Ethanol
Water for Injections

6.2 Incompatibilities

Melphalan medac is not compatible with infusion solutions containing dextrose and it is recommended that ONLY sodium chloride intravenous infusion 0.9 % w/v is used.

6.3 Shelf life

Unopened vial: 2 years

Once reconstituted the product should be used immediately. Any unused portion should be discarded.

Shelf life after reconstitution:
Chemical and physical in-use stability is limited and the solution should be prepared immediately before use. The reconstituted solution (5 mg/ml) should be transferred into the infusion bag in less than 30 minutes and the diluted solution should be completely administered within 1.5 hour of reconstitution.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light. Do not refrigerate.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder: Clear, type I glass vial (15 ml) with 20 mm grey colour bromo butyl igloo rubber stopper and 20 mm aluminium flip off light blue colour seals.

Solvent: Clear, type I glass vial (15 ml) with 20 mm grey colour bromo butyl rubber stopper and 20 mm aluminium flip off dark blue colour seals.

Pack size: Single pack containing 1 vial of powder and 1 vial of solvent.

6.6 Special precautions for disposal and other handling

Precautions
Melphalan IS AN ACTIVE CYTOTOXIC AGENT FOR USE UNDER THE DIRECTION OF PHYSICIANS EXPERIENCED IN THE ADMINISTRATION OF SUCH AGENTS. Caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.

Safe handling of Melphalan medac
The handling of Melphalan formulations should follow guidelines for the handling of cytotoxic drugs.

Preparation of Melphalan medac powder and solvent for solution for injection/infusion
Melphalan medac solution for injection/infusion should be prepared, at room temperature (approximately 25 °C), by reconstituting the freeze-dried powder with the solvent provided.

It is important that both the freeze-dried powder and the solvent provided are at room temperature before starting reconstitution. Warming the diluent in the hand may aid reconstitution. 10 ml of this vehicle should be added quickly, as a single quantity into the vial containing the freeze dried powder, and immediately shaken vigorously (for at least 120 seconds) until a clear colourless to clear light brown colour solution without visible particles, is obtained. Each vial must be reconstituted individually in this manner. The resulting solution contains the equivalent of 5 mg/ml melphalan and has a pH of approximately 6.5.

The reconstituted solution should be clear and practically free from visible particles.

Melphalan medac solution has limited stability and should be prepared immediately before use. Any solution unused after one hour should be discarded according to standard guidelines for handling and disposal of cytotoxic drugs.

If visible turbidity or crystallization occurs in the diluted solution for infusion, this solution should be discarded.

The reconstituted solution should not be refrigerated, as this will cause precipitation.

7 MARKETING AUTHORISATION HOLDER

medac Gesellschaft für klinische Spezialpräparate mbH
Theaterstrasse 6
22880 Wedel
Germany

8 MARKETING AUTHORISATION NUMBER

PA0623/019/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st May 2021

10 DATE OF REVISION OF THE TEXT

June 2022