SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Melphalan 50 mg concentrate and solvent for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Melphalan Injection is supplied as a unit pack comprising of a concentrate vial and solvent vial.

Each vial of 1 ml of concentrate contains melphalan hydrochloride equivalent to 50 mg melphalan.

After first dilution of the concentrate with 9 ml of the solvent, the concentration of melphalan is 5 mg/ml.

Excipients with known effect

When first diluted each vial contains 8.48 mmol (195 mg) of Sodium, 0.1 ml (103.3 mg) of propylene glycol and 2250 mg of Sulfobutyl-ether-β-cyclodextrin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate and solvent for solution for injection/infusion (sterile concentrate)

Concentrate:	Clear colourless to pale yellow solution.
Solvent:	Clear colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Melphalan Injection, at conventional intravenous dose, is indicated in the treatment of multiple myeloma and ovarian cancer.

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

In the above indications, Melphalan Injection may be used alone or in combination with other cytotoxic medicinal products.

4.2 Posology and method of administration

Parenteral administration:

Melphalan Injection is for intravenous use only.

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

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 total time from preparation of the injection solution to the completion of infusion should not exceed 1 hour.

Multiple myeloma:

Melphalan Injection 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 Injection 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.

Special populations

Use in Children

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.

Use in the 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 subgroup.

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 Injection in elderly patients.

Dosage in renal impairment

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 Tablets to patients with renal impairment, but it may be prudent to use a reduced dosage initially until tolerance is established.

When Melphalan Injection is used at conventional intravenous dosage (16-40 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 Injection (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 the therapeutic need. Melphalan Injection should not be given without haematopoietic stem cell rescue at doses 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.

<u>Method of administration</u>

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

Melphalan Injection 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 diluted solutions, the preparation must be discarded.

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

If high-dose Melphalan Injection is administered with or without transplantation (autologous bone marrow, allogenic or haematopoietic stem cell), administration via a

central venous line is recommended as extravasation and subsequent local tissue damage may occur if peripheral administration is used (see section 4.4).

Injection /infusion

For instructions on dilution of the medicinal product before administration, see section 6.6.

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

4.3 Contraindications

- Melphalan should not be given to patients who have suffered a previous hypersensitivity reaction to melphalan.
- Severe myelosuppression (leukocytes <2000 / mm^3, thrombocytes <50,000 / mm^3).

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.

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

Melphalan Injection 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 Injection 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 Injection should be confined to specialist centres, with the appropriate facilities and only be conducted by experienced clinicians.

In patients receiving high dose Melphalan Injection, 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 Injection. Melphalan Injection 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 practiced when either partner is receiving Melphalan.

Safe handling of Melphalan

The handling of Melphalan formulations should follow guidelines for the handling of cytotoxic drugs according to the Royal Pharmaceutical Society of Great Britain Working Party on the handling of cytotoxic drugs.

Monitoring

Since Melphalan is a potent myelosuppressive agent, it is essential that careful attention should be paid, both during and after treatment, 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 should be used with caution in patients who have undergone recent radiotherapy or chemotherapy in view of increased bone marrow toxicity.

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 Posology and Method of Administration). See Undesirable Effects 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

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 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.

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.

Solid tumours

The use of alkylating agents has been implicated in the development of secondary primary malignancies

Excipients with known effects

This medicinal product contains 195 mg sodium per vial (after first dilution, 50 mg/10 ml solution), equivalent to 9.75% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Solvent vial contains 2250 mg of Sulfobutyl-ether-β-cyclodextrin.

The drug contains the excipient 0.1 ml (103.3 mg) of propylene glycol which may cause alcohol-like symptoms. In case of hypersensitivity to this substance the administration is contraindicated.

Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.

While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. 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.

4.5 Interaction with other medicinal products and other forms of interaction

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see Special warnings and precautions for use).

Nalidixic acid together with high-dose intravenous melphalan has caused deaths in children due to haemorrhagic entercolitis.

Impaired renal function has been described in bone marrow transplant patients who received high dose intravenous melphalan and who subsequently received ciclosporin to prevent graft-versus-host disease.

4.6 Fertility, pregnancy and lactation

The teratogenic potential of Melphalan has not been studied. In view of its mutagenic properties and structural similarity to known teratogenic compounds, it is possible that melphalan could cause congenital defects in the offspring of patients treated with the drug.

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.

Mothers receiving Melphalan should not breastfeed.

4.7 Effects on ability to drive and use machines

None Known.

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 and <1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000.

<u>Blood and Lymphatic System Disorders</u>

Very	bone marrow depression leading to leucopenia,

common:	thrombocytopenia and anaemia
Rare:	haemolytic anaemia

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.

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 pretreatment 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

General Disorders and Administration Site Conditions

Very common:	subjective and transient sensation of warmth and/or tingling

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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Gastro-intestinal effects, including nausea, vomiting and diarrhoea are the most likely signs of acute oral overdosage. 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, 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, 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, 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% of 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/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 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.

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

Metabolism

In vivo and *in vitro* data suggest that spontaneous degradation rather than enzymatic metabolism is the major determinant of the medicinal product'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/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 i.v. 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 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 Dosage and Administration - Renal impairment and Warnings and Precautions – Renal impairment).*

Elderly

No correlation has been shown between age and melphalan clearance or with melphalan terminal elimination half-life *(see Dosage and Administration).*

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concentrate:

Monothioglycerol

Propylene glycol

Sodium chloride

Macrogol 400

Solvent:

Sulfobutylbetadex sodium

Sodium chloride

Sodium acetate trihydrate

Water for injections

6.2 Incompatibilities

Melphalan Injection 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 vial

2 years.

After first dilution of Melphalan 50 mg concentrate with 9 ml of the supplied solvent

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C and 1 hour at 25°C.

After further dilution of the concentrate-solvent mixture with sodium chloride 9 mg/ml (0.9%) solution for injection

Chemical and physical in-use stability of the solution in polyethylene containers diluted to 0.45 mg/ml has been demonstrated for 4 hours when stored at ambient temperature 25°C in addition to the 1-hour storage after first dilution at 25°C.

From a microbiological point of view, unless the method of opening and dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Keep the vials in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Concentrate

Clear glass vial (10 ml) with flurotec plus rubber stopper and an aluminium flip off seal containing 1 ml of concentrate. Vial is sheathed in a protective sleeve.

Solvent

Clear glass vial (10 ml) with flurotec plus rubber stopper and an aluminium flip off seal containing 9 ml of solvent.

Pack size: 1 vial of concentrate and 1 vial of solvent

6.6 Special precautions for disposal

Safe Handling of Melphalan

Melphalan should be prepared for administration either by or under the direct supervision of a pharmacist who is familiar with its properties and safe handling requirements.

Refer to local cytotoxic guidelines before commencing. For instructions on administration, see section 4.2.

Melphalan should be prepared for use in the aseptic unit of a pharmacy equipped with a suitable vertical laminar flow cabinet. Where such a facility is not available, a specially designated side room of a ward or clinic may be used.

Personnel preparing or handling Melphalan Injection should wear the following protective clothing.

- Disposable gloves of surgical latex or polyvinylchloride of a suitable quality (rubber gloves are not adequate);
- Surgical facemask of suitable quality;
- Protective goggles or glasses which should be washed thoroughly with water after use;
- Disposable apron.
- In an aseptic facility, other suitable clothing will be required.

Any spillage should be dealt with immediately (by personnel wearing suitable protective clothing), by mopping with damp, disposable paper towels which are placed in a high-risk waste disposal bag after use and disposed of in compliance with relevant local legislation. Contaminated surfaces should be washed with copious quantities of water.

Should melphalan solution come into contact with the skin, wash immediately and thoroughly with soap and plenty of cold water. In such instances it may be prudent to seek medical advice.

In case of contact with eyes, IMMEDIATE irrigation with sodium chloride eye wash should be carried out and medical attention sought without delay. If sodium chloride solution is not available, large volumes of water may be used.

Staff who are pregnant or trying to conceive should not handle melphalan.

Preparation of Melphalan Injection

(See also above, Safe Handling of Melphalan Injection).

Note: Both the Melphalan 50 mg concentrate and solvent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the entire contents of the accompanying solvent, there is solution containing 5 mg/ml melphalan.

Melphalan Injection should be prepared by first dilution with the solvent provided and second dilution with sodium chloride 9 mg/ml (0.9%) solution for injection. After first dilution of the concentrate with 9 ml of the solvent, the concentration of melphalan is 5 mg/ml. The preferred method of administration is injection of 5 mg/ml concentration solution into fast running infusion solution. If direct injection into a fast-running infusion is not appropriate, Melphalan Injection solution may be administered diluted in an infusion bag to obtain a final concentration between 0.45 and 4.0 mg/ml.

STEP 1: DILUTION OF THE CONCENTRATE VIAL WITH THE SUPPLIED SOLVENT

- Aseptically withdraw the **entire contents** of the supplied solvent
- Inject the **entire contents** of the solvent into the vial of Melphalan 50 mg concentrate.
- Mix the solvent and the concentrate well by inversion of the vial. It should also be noted that the mixing process may create a considerable amount of very small air bubbles. These bubbles may persist and may take a further 2 to 3 minutes to clear.
- The resulting 10 ml solution contains the equivalent of 5 mg/ml anhydrous melphalan and has a pH of approximately 4.5.
- The solution should be a clear colourless to pale yellow solution, free from visible particulate matter. If such a solution is not obtained it should be discarded (See Disposal, above).

STEP 2: DILUTION OF CONCENTRATE–SOLVENT MIXTURE IN SODIUM CHLORIDE 9 MG/ML (0.9%) SOLUTION FOR INJECTION

- Aseptically withdraw the required amount of concentrate-solvent mixture (containing melphalan 5 mg/ml) from the vial.
- Inject the withdrawn volume into appropriate volume of sodium chloride 9 mg/ml (0.9%) solution for injection and mix by inversion of the bag or bottle.
- The solution should be a clear colourless to pale yellow solution, free from visible particulate matter.

  The final diluted solution in the bag or bottle should be inspected visually for particulate matter prior to administration.

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. (Please refer to section 4.2).

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

The vials are for single use only.

Disposal

Melphalan should be disposed of in compliance with relevant local legislation. In the absence of such guidelines, the solution should be disposed of in a manner appropriate for toxic chemicals, for example, high-temperature incineration or deep burial.

Disposal of sharp objects, such as needles, syringes, administration sets and ampoules should be in rigid containers labelled with a suitable hazard warning seal. Personnel involved in disposal should be aware of the precautions to be observed, and the material should be destroyed by incineration if appropriate. All disposal must be in accordance with local regulatory requirements.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd

(Trading style: Accord)

Whiddon Valley

Barnstaple

Devon

EX32 8NS

8 MARKETING AUTHORISATION NUMBER

PL 00142/1285

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/06/2023

10 DATE OF REVISION OF THE TEXT

27/06/2023