SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

MELPHALAN RAZ 50 MG

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.

Each ml of the reconstituted solution contains 5 mg melphalan.

Excipient(s) with known effect:

After reconstitution:

Each vial contains 0.42 g ethanol and 6.21 g propylene glycol.

Each vial contains 53.50 mg sodium.

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/cake.

Solvent: A clear colourless solution.

pH of the reconstituted solution is between 6.0 and 7.0.

4. Clinical particulars

4.1. Therapeutic indications

For the palliative treatment of multiple myeloma and for the palliation of non resectable epithelial cancer of the ovary.

4.2. Posology and method of administration

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.

Since melphalan is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be delayed or adjusted if necessary (See section 4.4).

Posology

Parenteral administration:

For intravenous administration, it is recommended that MELPHALAN RAZ 50 MG solution 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 RAZ 50 MG solution may be administered diluted in an infusion bag.

Melphalan is not compatible with infusion solutions containing dextrose, and it is recommended that ONLY Sodium Chloride intravenous infusion 0.9% w/v is used.

When further diluted in an infusion solution, MELPHALAN RAZ 50 MG has reduced stability and the rate of degradation increases rapidly with rise in temperature. If administration occurs 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 crystallization appear in the reconstituted or diluted solutions, the preparation must be discarded.

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 (see section 4.4).

If high-dose MELPHALAN RAZ 50 MG is administered with or without haematopoietic stem cell rescue, administration via a central venous line is recommended.

Populations

- **Adults**

MULTIPLE MYELOMA

MELPHALAN RAZ 50 MG has been used on an intermittent basis alone, at doses varying between 8mg/m^2 and 30 mg/m^2 body surface area, given at intervals of between 2 to 6 weeks. Additionally, administration of prednisone has been included in a number of regimens. The literature should be consulted for precise details on treatment protocols.

A typical intravenous dosage schedule is 0.4 mg/kg bodyweight (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 I.V. doses of between 100 and 200 mg/m^2 body surface area (approximately 2.5 to 5.0 mg/kg bodyweight), but haematopoietic stem cell rescue becomes essential following doses in excess of 140 mg/m^2 body surface area. In cases of renal impairment, the dose should be reduced by 50% (see Renal impairment). In view of the severe myelosuppression induced by high-dose MELPHALAN RAZ 50 MG, treatment should be confined to specialist centers with the appropriate facilities, and only be administered by experienced clinicians (see section 4.4).

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.

- **Children**

Melphalan, within the conventional dosage range, is only rarely indicated in children and absolute dosage guidelines cannot be provided.

- **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 RAZ 50 MG in elderly patients.

The pharmacokinetics of intravenous melphalan has not shown a correlation between age and melphalan clearance or with melphalan terminal elimination half-life. The limited data available do not support specific dosage adjustment recommendations for elderly patients receiving intravenous melphalan and suggested that current practice of dosage adjustment based upon the general condition of the geriatric patient and the degree of myelosuppression incurred during therapy should be continued.

- **Renal impairment**

Melphalan clearance, though variable, is decreased in renal impairment (see also Warnings and Precautions-Renal impairment).

When MELPHALAN RAZ 50 MG is used at conventional intravenous dosage (8 to 40 mg/m^2 body surface area), it is recommended that the initial dose should be reduced by 50% in patients with moderate to severe renal impairment 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 reinfused, 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 without

haematopoietic stem cell rescue is not recommended 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.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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.
Melphalan should be administered under the direction of a specialist oncology service having the facilities for a regular monitoring of clinical biochemical and haematological effects during and after administration. In view of the hazards involved and the level of supportive care required, the administration of high-dose melphalan Injection should only be conducted by experienced clinicians.
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 receiving melphalan, up to three months for male patients and 6 months for female patients after end of treatment. For ovarian cancer, non-hormonal contraceptive methods are advised.

Monitoring

Bone marrow depression, with leucopenia and thrombocytopenia, is the main side effect. The time of maximum depression is variable, and careful attention should be paid to the monitoring of blood counts, both during and after treatment, to avoid the possibility of excessive myelosuppression and 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.

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.

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.

Neutropenia and thrombocytopenia

Elderly

Increased rate of haematological toxicities, particularly, neutropenia and thrombocytopenia, was observed in newly diagnosed elderly multiple myeloma in patients 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).

Mutagenicity

Melphalan is mutagenic in animals and chromosome aberrations have been observed in patients being treated with the drug. Melphalan has also been shown to be carcinogenic in animals (section 5.3), and the possibility of a similar effect should be borne in mind when designing the long-term management of the patient.

Suppression of ovarian function with resultant amenorrhoea occurs in a significant number of pre-menopausal patients. There is evidence from some animal studies that melphalan can have an adverse effect on spermatogensis. Therefore, it is possible that melphalan may cause temporary or permanent sterility in male patients.

Carcinogenicity

Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)

Melphalan, in common with other alkylating agents, has been reported to be leukaemogenic in man, especially in older patients after long combination therapy and radiotherapy.

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 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.

Risk must be balanced against the potential therapeutic benefit when considering the use of melphalan.

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 another reliable contraceptive method (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.

Renal Impairment

In patients with moderate to severe renal impairment the initial dose of the intravenous preparation should be reduced by 50% being determined thereafter according to haematological response. Such patients should be closely observed for uraemic marrow suppression. Temporary significant elevation of blood urea has been seen in the early stages of treatment in myeloma patients with renal damage (see sections 4.2 and 4.8).

Important information about other components:

5% Ethanol (alcohol)

This medicine contains 0.424g of alcohol (ethanol) in each 10 ml vial which is equivalent to 7.1 mg/kg (4.24% w/v).

The amount in 10 ml of this medicine is equivalent to less than 11 ml beer or 4 ml wine.

The small amount of alcohol in this medicine will not have any noticeable effects.

Propylene glycol

Propylene glycol in this medicine can have the same effects as drinking alcohol and increase the likelihood of side effects.

Do not use this medicine in children less than 5 years old.

Use this medicine only if recommended by a doctor. Your doctor may carry out extra checks while you are taking this medicine.

Sodium

This medicinal product contains 53.50 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

Live organism vaccines

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see section 4.4).

Nalidixic acid

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.

Busulfan

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.

Ciclosporin

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 ethanol 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 for male patients and 6 months for female patients after end 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 and particularly during the first trimester, unless considered absolutely essential by the physician. 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. Due to its mutagenic properties, melphalan is contraindicated during breastfeeding (see section 4.3).

Fertility

Melphalan causes suppression of ovarian function in premenopausal women resulting in amenorrhoea in a significant number of premenopausal 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 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).

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[1] and anaemia
	Rare	Haemolytic anaemia
Immune system disorders	Rare	Hypersensitivity[2] (see skin and subcutaneous tissue disorders)
Respiratory, thoracic and mediastinal disorders	Rare	Interstitial lung disease and pulmonary fibrosis (including fatal reports)
Gastrointestinal disorders	Very common	At high dose: nausea, vomiting and diarrhoea; stomatitis
	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 prurtitis (see also immune system disorders)
Musculoskeletal and connective tissue disorders[3]	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[4]
	Uncommon	Acute kidney injury
Reproductive system and breast disorders	Common	Azoospermia and amenorrhoea

Vascular disorders[5]	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
	Common	Mucosal inflammation (mucositis)

[1] Increased rate of haematological toxicities, particularly, neutropenia and thrombocytopenia, was observed in newly diagnosed elderly multiple myeloma in patients treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone (see sections 4.4).

[2] 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.

[3] Only with melphalan infusion after administration of regional perfusion in the limb.

[4] Temporary significant elevation of the blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage.

[5] 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 section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

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 with some immunosuppressant properties. 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 body weight, 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 sections 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, 13 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 at clinically relevant exposure levels 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 µM) 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 µg/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

Powder

Povidone

Hydrochloric acid

Solvent

Sodium citrate dihydrate

Propylene glycol

Ethanol 96 %

Water for injection

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: The expiry date of the product is indicated on the packaging materials.

Reconstituted Solution: Once reconstituted the product should be used immediately. Any unused portion should be discarded. The reconstituted solution should not be kept in the refrigerator since the active substance may precipitate. 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 total time from the preparation of reconstituted solution to the completion 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 but it is recommended to be stored in room temperature. 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 omniflex 3G coated bromobutyl rubber stopper and flip off aluminium seal having orange colour polypropylene button with matte finish.

Pack size: 1 vial containing 50 mg melphalan.

Solvent: Clear type I glass vial sealed with coated bromobutyl rubber stopper and flip off aluminium seal having orange colour polypropylene button with matte finish.

Pack size: 1 vial containing 10 ml sterile solvent.

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:

- The employees are to be instructed in the reconstitution of the drug.

- Pregnant women should be excluded from handling this medicine.

- The personnel should wear suitable protective clothing with face masks, safety goggles and gloves when reconstituting the preparation.

- 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 and Importer

RAZ PHARMACEUTICS LTD., 31 Gesher haetz St., Industrial Park, Emek Hefer, Israel.

8. LICENSE NUMBER

166-16-35540-00

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