יוני 2024

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,
חברת רז רוקחות מבקשת להודיעכם על עדכון העלון לצרכן של התכשיר: Melphalan Raz 50 mg
מרכיב פעיל: Melphalan (As Hydrochloride) 50mg
צורת מינון ומתן: Powder and solvent for solution for injection\infusion
התוויה מאושרת לתכשיר:
For the palliative treatment of multiple myeloma and for the palliation of non resectable epithelial cancer of the ovary.

בהודעה זו מצוינים רק הסעיפים בהם נעשו שינויים מהותיים בעלון לרופא.
התוספות סומנו בצבע כחול, החמרות סומנו בצהוב, מחיקות בקו חוצה אדום.
העלון המעודכן נשלח למשרד הבריאות לצורך פרסומו במאגר התרופות שבאתר משרד הבריאות: www.health.gov.il, וניתן לקבלו מודפס על ידי פנייה לבעל הרישום: רז רוקחות בע"מ, גשר בעץ 31, פארק עשיות עמק חפר,ישראל.

בברכה,
יבגני קבלרצי'ק
רוקח ממונה

עדכון עלון לרופא:

[…]

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 ~~of solvent~~ contains 0.42~~43~~ g ethanol and 6.21~~48~~ g propylene glycol.

Each vial ~~of solvent~~ 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.

[…]

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

~~- Severe myelosuppression (leukocytes <2000 / mm³, thrombocytes <50,000 / mm³).~~

~~- Melphalan should not be used during pregnancy, especially during the first trimester (see section 4.6).~~

- 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.
~~It should be prescribed only by physicians experienced in the management of malignant disease with such agents.~~
As with all high dose chemotherapy, precautions should be taken to prevent tumour lysis syndrome.

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

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

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

Melphalan ~~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 (see section 4.2).~~

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

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.

~~Haematological disorders (~~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.

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

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).

~~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. In patients with renal impairment who are treated with melphalan 50 mg i.v, blood urea levels may be transiently elevated and may cause bone marrow suppression. Therefore, blood urea levels should be carefully monitored in these patients.~~

~~Paediatric population~~

~~There is no adequate experience for children. Dose recommendations can not be given (see section 4.2).~~

Mutagenicity

~~Chromosome aberrations were observed in patients treated with melphalan.~~

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 ~~(secondary primary malignancy)~~

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

Melphalan, in common with other alkylating agents, has been reported to be leukaemogenic in man ~~can cause leukemia~~ especially in ~~elderly~~ older patients after long combination therapy and radio~~ation~~therapy.

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.

~~Before starting the treatment, the leukemogenic risk (AML and MDS) should be weighed against the possible therapeutic benefit when the use of melphalan in combination with thalidomide or lenalidomide and prednisone is considered (see section 5.3), as it has been demonstrated that these combinations lead to an elevated leukemic risk.~~

~~Before and during the treatment, the physicians must therefore carefully examine the patients in the context of the usual measurement procedures for early cancer detection and, if necessary, initiate therapy.~~

~~In patients with ovarian carcinoma who were treated with alkylating agents including melphalan, acute leukemia significantly increased with respect to a treatment group that did not receive such substances.~~

Solid tumours

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

Patient ~~The~~ characteristics ~~of the patient~~ (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 ~~assessed~~ evaluated prior to ~~the~~ melphalan administration ~~of melphalan.~~

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

Contraception

Due to ~~the~~ 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, ~~with multiple myeloma,~~ combined~~ation~~ oral contraceptive~~s~~ pills are not recommended. If a patient is currently ~~taking a~~ using combined~~ation~~ oral contraception~~ve~~, she should switch to another reliable contraceptive method (i.e. ovulation inhibitory progesterone-only pills such as ~~, such as a Gestagen monotherapy for example~~ desogestrel ~~containing tablets or a~~ barrier method etc). The risk of venous thromboembolism ~~persists~~ continues for 4-6 weeks after discontinuing~~ation of a~~ combined oral contraception~~ve~~.

~~For males treated with melphalan 50 mg i.v. it is recommended to avoid conception during treatment with melphalan and up to 6 months there after, and be counseled as to sperm conservation prior to initiation of therapy due to the possibility of therapy induced irreversible infertility.~~

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)

~~The ready-to-use concentrate for preparing an injection solution or infusion solution contains 5 volume % ethanol, i.e. up to 424.3 mg per dose equivalent to 4.79 ml beer or 1.99 ml wine per dose.~~

~~For patients addicted to alcohol, this quantity can be harmful to health.~~

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.

~~This must be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy.~~

~~The alcohol content in this medicinal product may alter the effects of other medicinal products.~~

~~The alcohol content in this medicinal product may impair the ability to drive and the ability to use machines (see section 4.7).~~

Propylene glycol

~~The drug contains the excipient propylene glycol which may cause alcohol-like symptoms. In case of hypersensitivity to this substance the administration is contraindicated.~~

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 ~~23~~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 ~~children and adolescents, treated with~~ the paediatric population, for the busulfan-melphalan regimen, ~~there were~~ it has been ~~reports~~ reported that the administration of melphalan ~~may have an influence on the development of toxicities within~~ less than 24 hours after the last oral busulfan administration may influence the development of toxicities ~~of busulfan.~~

Ciclosporin

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.

Ethanol: please refer to the paragraph on ~~Propylene glycol~~ 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

~~As with all chemotherapies containing cytostatics, appropriate contraceptive measures must be taken when one of the partners receive melphalan. If pregnancy occurs during treatment, the possibility of genetic counseling should be used.~~

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 has a mutagenic effect on the development of an embryo.~~ Melphalan should not be used during pregnancy and particularly~~, especially~~ 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.

~~. In the case of a vital indication for the treatment of a pregnant patient, medical advice should be given on the risk of harm to the child associated with the treatment.~~

Breast-feeding

~~Do not breastfeed during treatment with Melphalan.~~

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.

~~Melphalan has a mutagenic effect in animal models; in patients treated with the drug, chromosomal aberrations were observed. Therefore, men treated are advised not to produce a child during treatment with melphalan and up to 6 months afterwards, and to consult a sperm reserve before the start of treatment because of the possibility of an irreversible infertility caused by the treatment (see section 5.3).~~

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

4.7 Effects on ability to drive and use machines

~~No studies have been conducted on the effects on the viability and the ability to operate machines. However the possibility will have to be taken into consideration, that the alcohol quantity in these pharmaceutical medicinal product can impair the competency to drive and the ability to operate 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: ~~Adverse reactions are listed below by system organ class and frequency grouping. The frequencies are defined as follows:~~ 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 ~~events~~**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	~~Common~~	~~Acute leukemia (see also section 5.3) may occur after a generally long latency period, especially in patients with a higher age after prolonged combination therapy and radiotherapy~~
	Not known	Secondary ~~Acute~~ acute ~~M~~myeloid ~~L~~leukaemia ~~(AML)~~ and myelodysplastic syndrome~~s (MDS)~~ (see section 4.4)
Blood and lymphatic system disorders	Very common	Bone marrow depression, ~~which manifests as~~ leading to leuk~~ocyt~~openia, thrombocytopenia, neutropenia[1] and anaemia
	Rare	H~~a~~emolytic ~~A~~anaemia
		~~Since melphalan is a strongly myelosuppressive agent, careful monitoring of the blood values is imperative to avoid excessive bone marrow depression and the risk of irreversible bone marrow aplasia. Since the blood values can continue to drop even after termination of the therapy, the treatment should be interrupted at the first sign of an unusually severe drop in leukocyte or platelet values.~~

Immune system disorders	Rare	Hypersensitivity[2] ~~Allergic reactions~~ (see ~~also~~ skin and subcutaneous tissue disorders) ~~Allergic reactions such as urticaria, edema, rashes, and anaphylactic shock occur in the initial and follow-up treatment, especially in the case of intravenous melphalan treatment. Cardiac arrest has been reported in rare cases in connection with the allergic reactions.~~
Respiratory, thoracic and mediastinal disorders	Rare	Interstitial ~~pneumonia~~ lung disease and pulmonary fibrosis (including fatal ~~cases~~ reports)
Gastrointestinal disorders	Very common	~~Gastrointestinal symptoms such as~~ At high dose: nausea, ~~diarrhoea and~~ vomiting and diarrhoea; stomatitis ~~at high doses.~~
	Rare	Stomatitis ~~with~~ at conventional dose ~~The high incidence of diarrhoea, vomiting and stomatitis is dose-limiting at high intravenous melphalan doses in combination with autologous bone marrow transplantation. Pre-treatment with cyclophosphamide may reduce the severity of melphalan-induced gastrointestinal injury (The literature should be consulted for details).~~
Hepato-biliary disorders	Rare	Hepatic ~~impairment~~ disorders ranging from ~~pathological~~ abnormal liver function tests to clinical manifestations such as hepatitis and jaundice; ~~Liver vein~~ veno-~~occlusions~~ occlusive ~~after~~ disease following high-dose therapy
Skin and subcutaneous tissue disorders	Very common	Alopecia at ~~Hair loss with~~ high dose.
	Common	Alopecia ~~Hair loss~~ at conventional dose
	Rare	Maculopapular ~~exanthemia~~ rashes and ~~itching~~ pruritis (see also immune system disorders)
Musculoskeletal and connective tissue disorders[3] ~~(After parenteral administration for regional perfusion of the extremities)~~	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	~~Transient, markedly increased blood~~ Blood urea increased[4] ~~levels under a melphalan treatment during the first cycles of patients with renal impairment with multiple myeloma.~~
	Uncommon	Acute kidney injury
Reproductive system and breast disorders	Common	Azoospermia and ~~Amenorrhoea~~ amenorrhoea ~~(see section 4.4)~~
Vascular disorders [5]	Not known	Deep vein thrombosis and pulmonary embolism ~~embolus~~
General disorders and administration site conditions	Very common	Subjective and transient heat sensation of warmth and / or tingling ~~after administration of high doses of melphalan via a central venous catheter.~~
	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~~s 4.2 and~~ 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 ~~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 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% ~~of~~ 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 ~~After~~ hyperthermic (39°C) perfusion of the lower limb ~~perfusion~~ with ~~melphalan at~~ 1.75 mg/kg body weight, ~~in 11 patients with another tumor disease (advanced malignant melanoma),~~ mean volumes of distribution ~~for~~ at steady state and central compartment ~~distribution were~~ of 2.87 ± 0.8 ~~liters~~ litres and 1.01 ± 0.28 ~~liters~~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 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 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 ~~564.6~~ ± 182.9 ~~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 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

~~Reproductive toxicity~~

~~Treatment with melphalan has been associated with a reduction in ovarian function in premenopause patients. Amenorrhoea occurred in a significant number of cases. From some animal experiments, it can be concluded that melphalan affects spermatogenesis. It is therefore possible that melphalan causes a transient or permanent sterility in male patients.~~

~~There are no studies on teratogenicity. However, due to the mutagenic effect and the structural similarity with other alkylating substances with teratogenic potential, the risk of malformations in children can not be ruled out if a parent has been treated with melphalan.~~

Mutagenicity ~~and carcinogenicity~~

Melphalan is mutagenic in animals. ~~experiments. Chromosome aberrations were observed in melphalan treated patients. Melphalan has demonstrated carcinogenic potential in animal experiments.~~

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, intraperitoneally administered melphalan at a dose of 7.5 mg / kg showed reproductive effects attributable to cytotoxic effects in certain stages of spermatogenesis in males and induced dominant lethal mutations and hereditary translocations in post-meiotic germ cells, particularly in the mid to late phase of spermatogenesis.~~

~~A study was conducted to measure the effects of melphalan on the reproductive ability of female mice.~~

~~The female animals received a single intraperitoneal dose of 7.5 mg / kg melphalan and were then housed with untreated males for the majority of their reproductive life (at least 347 days after treatment).~~

~~Significant reduction in litter size was observed in the first interval after treatment, followed by almost complete recovery. Thereafter, a gradual decline in litter size was observed.~~

~~At the same time, a decline in the proportion of productive females was observed, which was associated with an induced reduction in the number of small follicles (see section 4.6).~~

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.

[…]

6.3 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 ~~of reconstitution solution~~ 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 the injection~~ reconstituted solution to the completion of infusion should not exceed 1.5 hours at room temperature (approximately 25°C).

[…]

6.5 Nature and contents of container

Powder: Clear type I ~~moulded~~ 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 ~~moulded~~ 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.

~~Preparation of melphalan powder and solvent for solution for injection/infusion:~~

~~It is important that both the powder and the solvent provided are at a room temperature (approximately 25°C) before starting reconstitution.~~

~~Melphalan should be prepared at a room temperature (approximately 25°C), by reconstituting the powder with the solvent- diluent provided.~~

~~10 ml of the solvent should be added quickly, as a single quantity into the vial containing the powder using a sterile needle (21 gauge or higher gauge size needle should be used for piercing of vial stopper during reconstitution, for smooth and effective penetration, not too fast or too rough, and nicely perpendicular to the stopper without twisting of the needle) and syringe. 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.~~

~~It should also be noted that shaking of the formulation leads to a significant amount of very small air bubbles. These bubbles can stay in place and it can take another 2 to 3 minutes before they dissolve, 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. Any reconstituted solution unused should be discarded according to standard guidelines for handling and disposal of cytotoxic medicinal products.~~

~~If visible turbidity or crystallization occurs in the diluted solution for infusion, this solution should be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local~~

~~requirements for cytotoxic medicinal products.~~

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.

[…]