ינואר 2021

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

חברת רז רוקחות מבקשת להודיעכם על עדכון העלון לרופא של התכשיר:

MELPHALAN RAZ 50 MG

POWDER AND SOLVENT FOR SOLUTION FOR I.V INJECTION/INFUSION

מרכיבים פעילים:

MELPHALAN (AS HYDROCHLORIDE) 50 MG

המאושר להתוויה:

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

העלון נבנה על סמך עלון התכשיר המאושר ב-UK ובהתאם להתוויה ומשטר המינון של תכשיר הייחוס בישראל ALKERAN. החמרות שנוספו ואינן מופיעות בעלון תכשיר הייחוס מסומנות בצהוב:

[.....]

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. 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.

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

Haematological disorders (Monitoring)

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.

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.

Carcinogenicity (secondary primary malignancy)

Acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS)

Melphalan can cause leukemia especially in elderly patients after long combination therapy and radiation therapy.

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 tumors

The use of alkylating agents has been implicated in the development of secondary primary malignancies (SPM). In particular, melphalan in combination with lenalidomide and prednisone and, to a lesser extent,
thalidomide and prednisone are associated with an increased risk of solid SPM in elderly patients with newly diagnosed multiple myeloma.
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 prior to the administration of melphalan.

Contraception

Due to the increased risk of venous thromboembolism in patients with multiple myeloma, combination oral contraceptives are not recommended. If a patient is currently taking a combination oral contraceptive, she should switch to another reliable contraceptive method, such as a Gestagen monotherapy for example desogestrel containing tablets or a barrier method. The risk of venous thromboembolism persists for 4-6 weeks after discontinuation of a combined oral contraceptive.
For males treated with melphalan 50 mg i.v. it is recommended to avoid conception during treatment with melphalan and up to 6 months thereafter, and be counseled as to sperm conservation prior to initiation of therapy due to the possibility of therapy induced irreversible infertility.

important information about other components, etc.

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 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).
The drug contains the excipient propylene glycol which may cause alcohol-like symptoms. In case of hypersensitivity to this substance the administration is contraindicated.
This medicinal product contains 53.5 mg sodium per vial, equivalent to 23% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

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

Nalidixic acid together with high-dose intravenous melphalan has caused deaths in children due to haemorrhagic enterocolitis.
In children and adolescents, treated with busulfan-melphalan regimen, there were reports that the administration of melphalan may have an influence on the development of toxicities within 24 hours after the last oral administration of busulfan.
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

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

Fertility

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

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.
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 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	Acute Myeloid Leukaemia (AML) and myelodysplastic syndromes (MDS)
Blood and lymphatic system disorders	Very common	Bone marrow depression, which manifests as leukocytopenia, thrombocytopenia and anaemia.
	Rare	Hemolytic 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	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 and pulmonary fibrosis (including fatal cases).
Gastrointestinal disorders	Very common	Gastrointestinal symptoms such as nausea, diarrhoea and vomiting, stomatitis at high doses.
	Rare	Stomatitis with 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 from pathological liver function to clinical manifestations such as hepatitis and jaundice; Liver vein occlusions after high-dose therapy.
Skin and subcutaneous tissue disorders	Very common	Hair loss with high dose.
	Common	Hair loss at conventional dose
	Rare	Maculopapular exanthemia and itching (see also immune system disorders).
Musculoskeletal and connective tissue disorders (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 urea levels under a melphalan treatment during the first cycles of patients with renal impairment with multiple myeloma.
Reproductive system and breast disorders	Common	Azoospermia and Amenorrhoea (see section 4.4)
Vascular disorders	Not known	Deep vein thrombosis, pulmonary embolus
General disorders and administration site conditions	Very common	Subjective and transient heat sensation and / or tingling after administration of high doses of melphalan via a central venous catheter.

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

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

5.2 Pharmacokinetic properties

Absorption

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

Melphalan is moderately bound to plasma proteins with reported percent binding ranging from 69% to 78%. There is evidence that the protein binding is linear in the range of plasma concentrations usually achieved in standard dose therapy, but that the binding may become concentration-dependent at the concentrations observed in high-dose therapy. Serum albumin is the major binding protein, accounting for about 55 to 60% 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 2-20 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.

After hyperthermic (39 °C) lower limb perfusion with melphalan at 1.75 mg / kg body weight in 11 patients with another tumor disease (advanced malignant melanoma), mean volumes for steady state and central compartment distribution were 2.87 ± 0.8 liters and 1.01 ± 0.28 liters, respectively.
Melphalan displays limited penetration of the blood-brain barrier. Several investigators have sampled cerebrospinal fluid and found no measurable drug. Low concentrations (~10% of that in plasma) were observed in a single high-dose study in children.

Biotransformation

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

Elimination

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

In 8 patients given a single bolus dose of 0.5 to 0.6 mg/kg bodyweight, the composite initial and terminal half-lives were reported to be 7.7 ± 3.3 min and 108 ± 20.8 min, respectively. Following injection of melphalan, monohydroxymelphalan and dihydroxymelphalan were detected in the patients' plasma, reaching peak levels at approximately 60 min and 105 min, respectively. A similar half-life of 126 ± 6 min was seen when melphalan was added to the patients' serum *in vitro* (37°C), suggesting that spontaneous degradation rather than enzymic metabolism may be the major determinant of the drug's half-life in man.

Following administration of a two-minute infusion of doses ranging from 5 to 23 mg/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- 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.

Elderly

No correlation has been shown between age and melphalan clearance or with melphalan terminal elimination half-life.

Renal impairment

Melphalan clearance may be decreased in renal impairment.

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

experiments.

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).

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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.

[……..]