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Package Leaflet: Information for the User

Melphalan 50 mg Powder and Solvent for Solution for Injection / Infusion
melphalan

Read all of this leaflet carefully before you start using this medicine
- Keep this leaflet. You may need to read it again.
- If you have any further questions about your illness or your medicine, ask your doctor or nurse.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

In this leaflet:

1 What Melphalan is and what it is used for

Melphalan injection contains a medicine called melphalan. This belongs to a group of medicines called cytotoxics (also called chemotherapy). Melphalan is used to treat cancer. It works by reducing the number of abnormal cells your body makes.

Melphalan is used for:
- **Multiple myeloma** – a type of cancer that develops from cells in the bone marrow called plasma cells. Plasma cells help to fight infection and disease by producing antibodies
- Advanced **cancer of the ovaries**
- **Childhood neuroblastoma** - cancer of the nervous system
- **Malignant melanoma** – skin cancer
- **Soft tissue sarcoma** – cancer of the muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body

Ask your doctor if you would like more explanation about these diseases.

2 Before you have Melphalan

Do not have Melphalan if:
- You are allergic (hypersensitive) to melphalan or any of the other ingredients of Melphalan injection (See section 6: Further information)

Do not have Melphalan if the above applies to you. If you are not sure, talk to your doctor or nurse before having Melphalan.

Take special care with Melphalan
Before you use Melphalan, tell your doctor or nurse if:
- you have had radiotherapy or chemotherapy, now or recently
- you have a kidney problem.

If you are not sure if any of the above apply to you, talk to your doctor or nurse before having Melphalan.

Taking other medicines

Please tell your doctor or nurse if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This includes herbal medicines.

In particular, tell your doctor or nurse if you are taking any of the following:
- other cytotoxic drugs (chemotherapy)
- nalidixic acid (an antibiotic used to treat urinary tract infections)
- ciclosporin (used to prevent rejection of organs or tissues following a transplant or to treat certain skin conditions like psoriasis and eczema or to treat rheumatoid arthritis).

Having vaccines while you are taking Melphalan
If you are going to have a vaccination speak to your doctor or nurse before you have it. This is because some vaccines (like polio, measles, mumps and rubella) may give you an infection if you have them whilst you are being treated with Melphalan.

Pregnancy and breast-feeding
Do not have Melphalan if you are planning to have a baby. This applies to both men and women. Melphalan may harm your sperm or eggs. Reliable contraceptive precautions must be taken to avoid pregnancy whilst you or your partner are having this injection. Ask your doctor for advice.

If you are already pregnant, it is important to talk to your doctor before having Melphalan.

Do not breast-feed while having Melphalan. Ask your doctor or midwife for advice.

3 How to have Melphalan

Melphalan should only be prescribed for you by a specialist doctor who is experienced in treating blood problems or cancer.

Melphalan injection can be given:
- as an infusion into your vein
- as a perfusion to a particular part of your body through an artery.

Your doctor will decide how much Melphalan you will have. The amount of Melphalan depends on:
- your body weight or body surface area (a specific measurement taking into account your weight and your size)
- other drugs you are having
- your disease
- your age
- whether or not you have kidney problems.

When you are given Melphalan, your doctor will take regular blood tests. This is to check the number of cells in your blood. Your doctor may sometimes change your dose as a result of these tests.

If you have more Melphalan than you need
Your doctor will give you Melphalan so it is unlikely that you will receive too much. If you think you have been given too much or have missed a dose, tell your doctor or nurse.

4 Possible side effects

Like all medicines, Melphalan can cause side effects, although not everybody gets them.

If you get any of the following, talk to your specialist doctor or go to hospital straight away:

- allergic reaction, the signs may include:
    - a rash, lumps or hives on the skin
    - swollen face, eyelids or lips
    - sudden wheeziness and tightness of the chest
    - collapse (due to cardiac arrest)
- any signs of fever or infection (sore throat, sore mouth or urinary problems)
- any **unexpected** bruising or bleeding or feeling extremely tired, dizzy or breathless, as this could mean that too few blood cells of a particular type are being produced
- if you **suddenly** feel unwell (even with a normal temperature)
- if your muscles are achy, stiff or weak **and** your urine is darker than usual or brown or red in colour – when you have Melphalan directly into your arm or leg.

Talk to your doctor if you have any of the following side effects which may also happen with this medicine:

Very common (affects more than 1 in 10 people)
- a drop in the number of blood cells and platelets
- feeling sick (nausea), being sick (vomiting) and diarrhoea
- mouth ulcers - with high doses of Melphalan
- hair loss - with high doses of Melphalan
- a tingling or warm feeling where Melphalan was injected
- problems with your muscles like wasting and aching – when you have Melphalan directly into your arm or leg

Common (affects less than 1 in 10 people)
- hair loss - with usual doses of Melphalan
- high levels of a chemical called urea in your blood – in people with kidney problems who are being treated for myeloma
- a muscle problem which can cause pain, tightness, tingling, burning or numbness – called compartment syndrome. This can happen when you have Melphalan directly into your arm or leg

Rare (affects less than 1 in 1,000 people)
- an illness where you have a low number of red blood cells as they are being destroyed prematurely – this can make you feel very tired, breathless and dizzy and can give you headaches or make your skin or eyes yellow
- lung problems which may make you cough or wheeze and make it difficult to breathe
- liver problems which may show up in your blood tests or cause jaundice (yellowing of the whites of eyes and skin)
- mouth ulcers – with normal doses of Melphalan
- skin rashes or itching skin

The following side effects also happen with Melphalan:
- leukaemia – cancer of the blood
- in women: your periods stopping

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5 How to store Melphalan

- Keep out of the reach and sight of children.
- Do not use Melphalan after the expiry date, which is stated on the pack after 'Exp'.

- Do not store Melphalan Injection above 30°C. Do not refrigerate. Keep the vial in the outer carton, to protect from light.
- Your Melphalan Injection will be prepared for use by a healthcare professional. Once prepared it should be used immediately and must not be stored or refrigerated.

6 Further information

What Melphalan contains
The active ingredient is melphalan. Each Melphalan injection contains 50 mg of melphalan. The other ingredients are povidone K12 and hydrochloric acid. Melphalan is dissolved in a diluent before being injected. The diluent contains water, sodium citrate, propylene glycol and ethanol.

What Melphalan looks like and contents of the pack
Each pack contains one Melphalan Injection vial and one Melphalan Injection Diluent vial.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation holder:
Aspen Pharma Trading Limited
3016 Lake Drive,
Citywest Business Campus,
Dublin24,
Ireland
Service-Tel: 0800 008 7392 (+44 1748 828 391)

Manufacturer: GlaxoSmithKline Manufacturing S.p.A, San Polo di Torrile, Parma, Italy

Other formats:

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:

0800 198 5000 (UK only).

Please be ready to give the following information:
Product name Melphalan Injection 50 mg Reference number PL 39699/ 0039

This is a service provided by the Royal National Institute of the Blind.

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Melphalan 50 mg Powder and Solvent for solution for Injection / Infusion
50 mg melphalan

To the Medical and Pharmaceutical Professions

Presentation
Melphalan Injection is supplied as a unit pack comprising a vial containing a freeze-dried powder and a vial of solvent-diluent. Each Melphalan vial contains the equivalent of 50 mg of melphalan, in the form of the hydrochloride, as a sterile, white to off-white, freeze-dried powder, which includes 20 mg povidone K12. Each vial of solvent-diluent provides 10 ml of buffer solution containing 60% v/v propylene glycol with sodium citrate and ethanol.

Uses
Melphalan Injection, administered by regional arterial perfusion, is indicated in the treatment of localised malignant melanoma of the extremities and localised soft tissue sarcoma of the extremities.
Melphalan Injection, at conventional intravenous dosage, may be used in the treatment of:
multiple myeloma*:* Melphalan Injection, either alone or in combination with other cytotoxic drugs, is as effective as the oral formulation in the treatment of multiple myeloma;
ovarian cancer*:* Melphalan Injection produces an objective response in approximately fifty percent of the patients with advanced ovarian adenocarcinoma, when given alone, or in combination with other cytotoxic drugs.
Melphalan Injection, at high intravenous dosage, may be used in the treatment of:
multiple myeloma*:* complete remissions have been achieved in up to fifty percent of patients given high dose Melphalan Injection, with or without autologous bone marrow rescue, either as first line treatment or to consolidate a response to conventional cytoreductive chemotherapy;
neuroblastoma in childhood*:* high dose Melphalan Injection with autologous bone marrow rescue has been used either alone, or combined with radiotherapy and/or other cytotoxic drugs, to consolidate a response to conventional treatment. A significant increase in the duration of disease-free survival was demonstrated in a prospective randomised trial of high dose Melphalan Injection versus no further treatment.

Dosage and 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 *Precaution*s).
Multiple myeloma*:* Melphalan Injection has been used on an intermittent basis alone, or in combination with other cytotoxic drugs, at doses varying between 8 mg/m2 body surface area and 30 mg/m2 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.

When used as a single agent, a typical intravenous dosage schedule is 0.4 mg/kg body weight (16 mg/m2 body surface area) repeated at appropriate intervals (e.g. once every 4 weeks), provided there has been recovery of the peripheral blood count during this period.
High-dose regimens generally employ single intravenous doses of between 100 and 200 mg/m2 body surface area (approximately 2.5 to 5.0 mg/kg body weight), but autologous bone marrow rescue becomes essential following doses in excess of 140 mg/m2 body surface area.
In cases of renal impairment, the dose should be reduced by fifty percent. (see *Dosage in renal impairmen*t). In view of the severe myelosuppression induced by high dose Melphalan Injection, treatment should be confined to specialist centres, with the appropriate facilities, and only be administered by experienced clinicians (see *Precaution*s).
Ovarian adenocarcinoma*:* When used intravenously as a single agent, a dose of 1 mg/kg body weight (approximately 40 mg/m2 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/m2 body surface area) have been used at intervals of 4 to 6 weeks.
Malignant melanoma*:* Hyperthermic regional perfusion with Melphalan has been used as an adjuvant to surgery for early malignant melanoma and as palliative treatment for advanced but localised disease. The scientific literature should be consulted for details of perfusion technique and dosage used. A typical dose range for upper extremity perfusions is 0.6 to1.0 mg/kg body weight and for lower extremity perfusions is 0.8 to 1.5 mg/kg body weight.
Soft tissue sarcoma*:* Hyperthermic regional perfusion with Melphalan has been used in the management of all stages of localised soft tissue sarcoma, usually in combination with surgery. Melphalan has also been given with actinomycin D and the scientific literature should be consulted for details of dosage regimens. A typical dose range for upper extremity perfusions is 0.6 to1.0 mg/kg body weight and for lower extremity perfusions is 1.0 to1.4 mg/kg body weight.
Advanced neuroblastoma*:* Doses of between 100 and 240 mg/m2 body surface area (sometimes divided equally over 3 consecutive days) together with autologous bone marrow rescue, have been used either alone or in combination with radiotherapy and/or other cytotoxic drugs.

Preparation of Melphalan Injection Solution*:* Melphalan Injection should be prepared, AT ROOM TEMPERATURE, by reconstituting the freeze-dried powder with the Solvent-Diluent provided.
10 ml of the vehicle should be added quickly, as a single quantity into the vial containing the freeze-dried powder, and immediately shaken VIGOROUSLY (for at least 50 seconds) until a clear solution, without visible particles, is obtained. Each vial must be reconstituted individually in this manner.The resulting solution contains the equivalent of 5 mg per ml anhydrous melphalan and has a pH of approximately 6.5.
Melphalan Injection solution has limited stability and should be prepared immediately before use. Any unused solution remaining after one hour should be discarded. (See *Pharmaceutical precaution*s).
The reconstituted solution should not be refrigerated as this will cause precipitation.
Parenteral administration*:* Except in cases where regional arterial perfusion is indicated, Melphalan Injection is for intravenous use only.
For intravenous administration it is recommended that Melphalan Injection 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 Injection 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 Injection 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.
If high dose Melphalan Injection is administered with or without autologous bone marrow transplantation, administration via a central venous line is recommended.
For regional arterial perfusion, the literature should be consulted for detailed methodology.
Use in children*:* Melphalan, at conventional dosage, is only rarely indicated in children and dosage guidelines cannot be stated.
High dose Melphalan Injection, in association with bone marrow rescue, has been used in childhood neuroblastoma and dosage guidelines based on body surface area, as for adults, may be used.
Use in the elderly*:* Although Melphalan is frequently used at conventional dosage in the elderly, there is no specific information available relating to its administration to this patient 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 Injection in elderly patients.
Dosage in renal impairment*:* Melphalan clearance, though variable, is decreased in renal impairment.
When Melphalan Injection is used at conventional intravenous dosage (8 to40 mg/m2 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/m2 body surface area), the need for dose reduction depends upon the degree of renal impairment, whether autologous bone marrow stem cells are reinfused, and therapeutic need. As a guide, for moderate to severe renal impairment (EDTA clearance 30 to 50 ml/min) a dose reduction of 50% is usual. Adequate hydration and forced diuresis are also necessary. High dose Melphalan is not recommended in patients with more severe renal impairment (EDTA clearance less than 30 ml/min).
Contra-indications, warnings, etc
Contra-indications*:* Melphalan should not be given to patients who have suffered a previous hypersensitivity reaction to melphalan.
Precautions*:* MELPHALAN IS AN ACTIVE CYTOTOXIC AGENT FOR USE UNDER THE DIRECTION OF PHYSICIANS EXPERIENCED IN THE ADMINISTRATION OF SUCH AGENTS.
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 may cause local tissue damage should extravasation occur, and consequently it should not be administered by direct injection into a peripheral vein. It is

recommended that Melphalan Injection solution is administered by injecting slowly into a fast-running intravenous infusion via a swabbed injection port, or via a central venous line.
In view of the hazards involved and the level of supportive care required, the administration of high dose Melphalan Injection should be confined to specialist centres, with the appropriate facilities, and only be conducted by experienced clinicians.
In patients receiving high dose Melphalan Injection, consideration should be given to the prophylactic administration of anti-infective agents, the administration of blood products as required, and the maintenance of a high renal output during the period immediately following the administration of Melphalan by the use of hydration and forced diuresis.
Consideration should be given to ensure adequate performance status and organ function before using high dose Melphalan Injection.
Safe handling of Melphalan*:* The handling of Melphalan formulations should follow guidelines for the handling of cytotoxic drugs according to the Royal Pharmaceutical Society of Great Britain Working Party on the Handling of Cytotoxic Drugs.
Monitoring*:* Since Melphalan is a potent myelosuppressive agent, it is essential that careful attention should be paid 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 bone marrow suppression.
Dose reduction may therefore be necessary (see *Dosage and administratio*n), and these patients should be closely observed (See *Side and adverse effects* for elevation of blood urea).
Mutagenicity*:* Melphalan is mutagenic in animals and chromosome aberrations have been observed in patients being treated with the drug. ***Carcinogenicity****:* Melphalan, in common with other alkylating agents, has been reported to be leukaemogenic. There have been reports of acute leukaemia occurring after melphalan treatment for diseases such as amyloid, malignant melanoma, multiple myeloma, macroglobulinaemia, cold agglutinin syndrome and ovarian cancer.
A comparison of patients with ovarian cancer who received alkylating agents with those who did not showed that the use of alkylating agents, including melphalan, significantly increased the incidence of acute leukaemia.
The leukaemogenic risk must be balanced against the potential therapeutic benefit when considering the use of melphalan.
Effects on fertility*:* Melphalan causes suppression of ovarian function in premenopausal women resulting in amenorrhoea in a significant number of patients.
There is evidence from some animal studies that Melphalan can have an adverse effect on spermatogenesis. Therefore, it is possible that Melphalan may cause temporary or permanent sterility in male patients.
Use in pregnancy and lactation*:* The teratogenic potential of Melphalan has not been studied. In view of its mutagenic properties and structural similarity to known teratogenic compounds, it is possible that melphalan could cause congenital defects in the offspring of patients treated with the drug.
As with all cytotoxic chemotherapy, adequate contraceptive precautions should be practised when either partner is receiving Melphalan.

The use of melphalan should be avoided whenever possible during pregnancy, particularly during the first trimester. In any individual case the potential hazard to the foetus must be balanced against the expected benefit to the mother.
Mothers receiving Melphalan should not breast-feed.
Side and adverse 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. Classification of frequency:- Very common ≥1/10, common ≥1/100, <1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000.

- **Blood and lymphatic system disorders**: very common: bone marrow depression leading to leucopenia, thrombocytopenia, anaemia; rare: haemolytic anaemia.
- **Immune system disorders**: rare: allergic reactions - urticaria, oedema, skin rashes and anaphylactic shock have been reported uncommonly following initial or subsequent dosing, particularly after intravenous administration. Cardiac arrest has also been reported rarely in association with such events.
- **Respiratory, thoracic and mediastinal disorders**: rare: interstitial pneumonitis and pulmonary fibrosis (including fatal reports).
- **Gastrointestinal disorders**: very common: nausea, vomiting and diarrhoea; stomatitis at high dose; rare: stomatitis at conventional dose. 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. Consult the literature for details.
- **Hepatobiliary disorders**: rare: hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice; veno-occlusive disease following high dose treatment.
- **Skin and subcutaneous tissue disorders**: very common: alopecia at high dose; common: alopecia at conventional dose; rare: maculopapular rashes and pruritus.
- **Musculoskeletal and connective tissue disorders**: Injection, following isolated limb perfusion: very common: muscle atrophy, muscle fibrosis, myalgia, blood creatine phosphokinase increased; common: compartment syndrome; incidence not known: muscle necrosis, rhabdomyolysis.
- **Renal and urinary disorders**: common: temporary significant elevation of the blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage.
- **General disorders and administration site conditions**: very common: subjective and transient sensation of warmth and/or tingling.

Drug interactions: Nalidixic acid together with high-dose intravenous melphalan has caused deaths in children due to haemorrhagic enterocolitis.Impaired renal function has been described in bone marrow transplant patients who were conditioned with high dose intravenous melphalan and who subsequently received ciclosporin to prevent graft-versus-host disease.
Toxicity and treatment of overdosage: The immediate effects of acute intravenous overdosage are nausea and vomiting. Damage to the gastro-intestinal mucosa may also ensue, and diarrhoea, sometimes haemorrhagic, has been reported after overdosage. The principal toxic effect is bone marrow suppression, leading to leucopenia, thrombocytopenia and anaemia.

General supportive measures, together with appropriate blood and platelet transfusions, should be instituted if necessary and consideration given to hospitalisation, antibiotic cover, and the use of haematological growth factors.
There is no specific antidote. The blood picture should be closely monitored for at least four weeks following overdosage until there is evidence of recovery.

Pharmaceutical precautions
Injection unit pack: Store below 30°C. Protect from light. Do not refrigerate.
Melphalan Injection surplus to requirements should be destroyed in a manner appropriate to the prevailing local regulatory requirements for the disposal of cytotoxic drugs.

Legal category
POM

Package quantities
Injection unit pack: Vial of Melphalan freeze-dried powder and vial of solvent-diluent.

Further information
Nil

Product licence numbers
Injection: PL 39699/ 0039
Solvent-Diluent: PL 39699/ 0040

The leaflet was last revised in August 2014

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