PACKAGE LEAFLET

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 because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.

- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Melphalan is and what it is used for

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

Melphalan injection 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**
- **Advanced neuroblastoma** - (a type of cancer affecting the nervous system) **in children**
- **Malignant melanoma** – a type of 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.

You must talk to a doctor if you do not feel better or if you feel worse.

2. What you need to know before you take Melphalan

Do not take Melphalan if:
- You are allergic to melphalan or any of the other ingredients of this medicine (listed in section 6).
- You are breastfeeding.

If you are not sure, talk to your doctor or nurse before having Melphalan.

Warnings and precautions
Before you use Melphalan, tell your doctor or nurse if:

- you have had radiotherapy or chemotherapy, now or recently,
- you have a kidney problem,
- you are going to have a vaccination or were recently vaccinated. 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.
- you are using combined oral contraception (the pill). This is because of the increased risk of venous thromboembolism in patients with multiple myeloma. You should switch to ovulation inhibitory progesterone-only pills (i.e., desogestrel). The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception.
- you are planning for a baby. This is because of the risk of gene toxicity (damage of genetic information) and infertility (see Pregnancy, Breastfeeding and Fertility).

Melphalan could increase the risk of developing other types of cancer (eg secondary solid tumours) in a small number of patients, particularly when used in combination with lenalidomide, thalidomide and prednisone. Your doctor should carefully evaluate the benefits and risks when you are prescribed Melphalan.

Other medicines and Melphalan
Please tell your doctor or nurse if you are taking, have recently taken or might take 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:
- vaccines which contain live organisms (see Warnings and precautions)
- 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).
- In children, busulfan (anti-cancer medicine)

Pregnancy, breast-feeding and fertility

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Do not have Melphalan if you are planning to have a baby. This applies to both men and women. Reliable and effective contraceptive precautions must be taken to avoid pregnancy whilst you or your partner are having this injection.
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 for advice.

Female patients should use effective and reliable contraceptive methods during treatment and for a period of six months following the cessation of treatment.

Male patients should use effective and reliable contraceptive methods during treatment and for a period of three months following the cessation of treatment.

Fertility
Melphalan can affect ovaries or sperm, which may cause infertility (inability to have a baby). In woman, menstruation can stop (amenorrhoea) and in men, a complete lack of sperm can be observed (azoospermia). Due to the possibility of the lack of sperm as a result of Melphalan treatment it is advised for men to have a consultation on sperm preservation before treatment.

Driving and using machines

Effects on the ability to drive and operate machinery in patients taking this medicine have not been studied.

Melphalan contains sodium.
This medicinal product contains 2mmol (46 mg) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

Melphalan contains ethanol.
This medicinal product contains 5 % ethanol (alcohol), equivalent to 10 ml beer or 2.4 ml wine. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

Melphalan contains propylene glycol.
May cause alcohol-like symptoms.

3. How to take Melphalan

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

Thromboembolic events
You should receive prophylaxis of venous thromboembolism for at least the first 5 months of treatment especially if you have additional thrombotic risk factors. Your doctor will decide what measures should be taken after careful assessment of your underlying risk factors.

If you experience any thromboembolic event, tell your doctor immediately as your treatment must be discontinued and a standard anticoagulation therapy started. Your doctor will decide if you should restart melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone once the thromboembolic events have been managed. You should continue anticoagulation therapy during the course of melphalan treatment.

If you have been given more Melphalan than you should
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, this medicinecan 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

Not known: (frequency cannot be estimated from the available data)
- leukaemia - cancer of the blood
- in women: your periods stopping (amenorrhoea)
- in men: absence of sperms in the semen (azoospermia)
- death of muscle tissue (muscle necrosis)
- deep vein thrombosis (formation of a blood clot called thrombus within a deep vein, predominantly in the legs) and pulmonary embolism (a blockage of the lung's main artery or its branches by a blood clot that breaks off and travels to the lung)
- acute kidney injury – kidney failure (significant reduction of kidney function) that happens within a short time

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.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Melphalan
- Keep this medicine out of the sight and reach 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. Contents of the pack and other information

What Melphalan contains
The active substance 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,
Dublin 24,
Ireland
Service-Tel: 0800 008 7392 (+44 1748 828 391)

Manufacturer:
Cenexi - Laboratories Thissen S.A., Rue de la Papyree 2-4-6, Braine-L'Alleud, 1420, Belgium

Medical Information Enquiries
For any Medical Information enquiries about this product, please contact: 24 Hour Helpline +441748 823 391 (free phone UK only 0800 0087 392).

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 Powder and Solvent for Solution for Injection/Infusion.
Reference number:
Injection: PL 39699/ 0039
Solvent-diluent: PL 39699/0040

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.

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).
Thromboembolic events: Thromboprophylaxis should be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors (see *Precautions and Side and adverse effects*).
If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment

and any complications of the thromboembolic event have been managed, melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone may be restarted at the original dose dependent upon a benefit-risk assessment. The patient should continue anticoagulation therapy during the course of melphalan treatment.

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. It is important that both the freeze-dried powder and the solvent provided are at room temperature before starting reconstitution. Warming the diluent in the hand may aid reconstitution. If the solvent-diluent is used at cold temperature, mephalan powder may not reconstitute properly and undissolved particles may be observed.

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. Slow diluents addition and delaying the shaking may lead to the formation of insoluble particles. It should be also noticed that the shaking process creates a considerable amount of very small air bubbles. These bubbles may persist and may take further 2 or 3 minutes to clear, as the resulting solution is quite viscous. This could make difficult the evaluation on solution clearness. 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.
Paediatric population*:* Melphalan, at conventional dosage, is only rarely indicated in paediatrics 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.
Elderly population*:* Although Melphalan is frequently used at conventional dosage in older people, there is no specific information available relating to its administration to this patient sub-group. Experience in the use of high dose Melphalan in older patients is limited. Consideration should therefore be given to ensure adequate performance status and organ function before using high dose Melphalan Injection in older patients.
Dosage in renal impairment*:* Melphalan clearance, though variable, is decreased in renal impairment. When Melphalan Injection is used at conventional intravenous dosage (16 to 40 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).

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

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