Package leaflet: Information for the patient

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.
- 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 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).

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 are given Melphalan

You should NOT be given Melphalan if any of following apply to you. Tell your doctor if:
- you are allergic to melphalan or any of the other ingredients of this medicine (listed in section 6)
- you are breastfeeding.

Warnings and precautions
Before treatment with Melphalan, tell your doctor if any of the following apply to you:
- 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 have a blood clot in your leg (thrombosis), lung (pulmonary embolism) or any other part of

your body, or have ever had it
- you have a condition that gives you an increased chance of getting a blood clot in you arteries
- men who are receiving Melphalan should not father a child during treatment and up to 3 months afterwards.

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 SUN.

Other medicines and Melphalan
Tell your doctor or nurse if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
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 following a transplant, to treat certain skin conditions like psoriasis and eczema or to treat rheumatoid arthritis)
- vaccines which contain live organisms (see Warnings and precautions)
- in children, busulfan (used to treat certain type of cancer).

Pregnancy, breastfeeding and fertility

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before this medicine is given.

Pregnancy
Treatment with Melphalan is not recommended during pregnancy because it may cause permanent damage to a foetus. If you are already pregnant, it is important to talk to your doctor before being given Melphalan. Your doctor will consider the risks and benefits to you and your baby of treatment with Melphalan.

Reliable contraceptive precautions must be taken to avoid pregnancy whilst you or your partner are having this injection/infusion.

Breastfeeding
It is unknown whether Melphalan is excreted in human breast milk. Do not breastfeed while being given Melphalan.

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

Male and female contraception
It is recommended that men who are receiving Melphalan do not father a child during treatment and up to 3 months afterwards. Talk to your doctor if you would like to use effective and reliable contraceptives.

Driving and using machines
Effects on the ability to drive and operate machinery in patients taking this medicine have not been studied. It is not expected that this medicine will affect the ability to drive or operate machines.

Melphalan contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

Melphalan contains ethanol (alcohol)
This medicine contains 5% ethanol (alcohol), equivalent to 10 ml beer or 2.4 ml wine per dose. Harmful for those suffering from alcoholism.
To be taken into account in pregnant or breastfeeding 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 Melphalan will be given

Melphalan will only be given to you by doctors or nurses experienced in giving chemotherapy.

Method of administration
Melphalan can be given
- as an infusion (drip) into your vein
- into an artery, administered to a certain body part (perfusion).

How much Melphalan is given
Your doctor will decide how much Melphalan you will be given. 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 change your dose as a result of these tests.

Risk of blood clots *(thromboembolic events)*
Your doctor will decide if you should receive a preventive treatment for blood clots in the veins. This applies during the first 5 months of treatment, or if you have an increased risk for developing a blood clot in the veins.

Use in children
Melphalan is only rarely used in children. Dosing guidelines for children are not available.

Use in elderly
There are no specific dosage adjustments for the elderly.

Use in patients with impaired renal function
If you have a kidney problem, your doctor will usually give you a lower dose than other adults.

If you are 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.

If you forget to use Melphalan
Your doctor will give you Melphalan so it is unlikely that you will miss a dose of this medicine. If you think you have missed a dose, skip that dose and you will be given next dose at the next prescribed time. Do not use a double dose to make up for a forgotten dose.

If you stop using Melphalan
If you feel you should stop using this medicine, consult your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

Serious side effects
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 are given Melphalan directly into your arm or leg.

Tell your doctor immediately if you have symptoms of blood clots in the veins, especially in the legs. Symptoms include swelling, pain and reddening of the leg. Blood clots can travel through the blood vessels to the lungs, causing pain on the chest and difficulties in breathing.

Other side effects include:

Very common side effects (may affect more than 1 in 10 people)
- fever
- a fall 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 are given Melphalan directly into your arm or leg.

Common side effects (may affect up to 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 are given Melphalan directly into your arm or leg.

Rare side effects (may affect up to 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 sperm in the semen (azoospermia)
- death of muscle tissue (muscle necrosis)
- breakdown of muscle fibers (rhabdomyolysis)
- formation of a blood clot, a so-called thrombus, in a deep vein, especially in the legs (deep venous thrombosis) and closure of a pulmonary artery (pulmonary embolism).
- secondary solid tumours.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. 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 or search for MHRA Yellow Card in the Google Play or Apple App Store. 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 this medicine after the expiry date which is stated on the label and the outer packaging after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C. Do not refrigerate. Keep the vial in the outer carton in order to protect from light.

Your Melphalan will be prepared for use by a healthcare professional. Once prepared it should be used immediately and must not be stored or refrigerated.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Melphalan contains
- The active ingredient is melphalan hydrochloride. Each vial contains melphalan hydrochloride equivalent to 50 mg melphalan.
- The other ingredients are povidone and hydrochloric acid. Melphalan is dissolved in 10 ml of solvent before being injected. The solvent contains water for injections, sodium citrate, propylene glycol and ethanol anhydrous.

What Melphalan looks like and contents of the pack
Each pack Melphalan contains one vial of Melphalan powder and one vial of solvent. The powder vial contains 50 mg of the active substance mephalan in a powder format and the solvent vial contains 10 ml of solvent in which to reconstitute (dissolve) the powder. The powder is a white to off-white

freeze-dried powder or cake and the solvent is a clear colourless liquid/solution. After reconstitution with 10 ml of the solvent, the resultant solution contains 5 mg/ml melphalan.

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This medicinal product is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

Austria:	Melphalan SUN
Denmark:	Melphalan SUN
Germany:	Melphalan SUN
France:	Melphalan SUN
Italy:	Melfalan SUN
Netherlands:	Melfalanhydrochloride SUN
Norway:	Melphalan SUN
Sweden:	Melfalan SUN
United Kingdom (Northern Ireland):	Melphalan

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The following is intended for healthcare professionals only

Safe Handling of Melphalan:
Melphalan should be prepared for administration by a trained professional who is familiar with its properties and safe handling requirements. Refer to local cytotoxic guidelines before commencing. For instructions on administration, see Section 4.2.
Melphalan should be prepared for use in the aseptic unit of a pharmacy equipped with a suitable vertical laminar flow cabinet. Where such a facility is not available, a specially designated side room of a ward or clinic may be used.

Personnel preparing or handling Melphalan should wear the following protective clothing:
Disposable gloves of surgical latex or polyvinylchloride of a suitable quality (rubber gloves are not adequate);
Surgical facemask of suitable quality;
Protective goggles or glasses which should be washed thoroughly with water after use;
Disposable apron.
In an aseptic facility, other suitable clothing will be required.

Any spillage should be dealt with immediately (by personnel wearing suitable protective clothing), by mopping with damp, disposable paper towels which are placed in a high-risk waste disposal bag after use and disposed of in compliance with relevant local legislation. Contaminated surfaces should be washed with copious quantities of water.

Should Melphalan solution come into contact with the skin, wash immediately and thoroughly with soap and plenty of cold water. In such instances it may be prudent to seek medical advice.

In case of contact with eyes, IMMEDIATE irrigation with sodium chloride eye wash should be carried out and medical attention sought without delay. If sodium chloride solution is not available, large volumes of water may be used.

Staff who are pregnant or trying to conceive should not handle Melphalan.

Preparation of Melphalan solution:
Melphalan should be prepared at 25°C, by reconstituting the freeze-dried powder/cake with the solvent-diluent provided.

Reconstitution
It is important that both the freeze-dried powder/cake and the solvent provided are at room temperature before starting reconstitution. Warming the diluent in the hand may aid reconstitution. 10 ml of this vehicle should be added quickly, as a single quantity into the vial containing the freeze dried powder, and immediately shaken vigorously (for approximately 1 minute) 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.

Vial size	Volume of diluent to be added to vial	Approximate available volume	Nominal concentration per ml
50 mg	10 ml	10 ml	5 mg/ml

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

Immediately withdraw reconstituted solution having concentration of 5 mg/ml of anhydrous melphalan from reconstituted vial and add using 10 ml new syringe into infusion bag containing of 0.9% Sodium Chloride Intravenous Infusion. Mix this diluted solution thoroughly by manual rotation 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 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.

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.

Should any visible turbidity or crystallisation appear in the reconstituted or diluted solutions the preparation must be discarded.

Disposal

Any solution unused after one hour should be discarded according to standard guidelines for handling and disposal of cytotoxic drugs.

Disposal of sharp objects, such as needles, syringes, administration sets and ampoules should be in rigid containers labelled with a suitable hazard warning seal. Personnel involved in disposal should be aware of the precautions to be observed, and the material should be destroyed by incineration if appropriate.