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, pharmacist 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
2. What you need to know before you use Melphalan
3. How to use Melphalan
4. Possible side effects
5. How to store Melphalan
6. Contents of the pack and other information

1. WHAT MELPHALAN IS AND WHAT IT IS USED FOR

Melphalan contains an active substance called melphalan and 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. WHAT YOU NEED TO KNOW BEFORE YOU USE MELPHALAN

Do not use Melphalan:
- if you are allergic to melphalan or any of the other ingredients of this medicine (listed in section 6).
- if you are breastfeeding (see section "Pregnancy, breast-feeding and fertility").

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

Warnings and precautions

Talk to your doctor or nurse before given Melphalan
- if you have had radiotherapy or chemotherapy, now or recently
- if you have a kidney problem
- if you are going to have a vaccination or were recently vaccinated (see "Vaccinations")
- if you are using combined oral contraception (the pill). This is because of the increased risk of venous thromboembolism (a blood clot that forms in a vein and migrates to another location) in patients with multiple myeloma (see Pregnancy, breast-feeding 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.

Thromboembolic events

An increased risk of 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) may occur when melphalan is used in combination with other medicines which can affect how your immune system works (such as lenalidomide/thalidomide) and others which can increase the benefits of the treatment with melphalan (such as prednisone/dexamethasone).

Your doctor will decide what measures should be taken after careful assessment of your underlying risk factors (such as smoking, increased blood pressure, high levels of lipids in the blood, history of thrombosis).

Reduction in white blood cells and in blood platelets

An increase in the number of blood toxicities, such as neutropenia (decrease of the number of white blood cells, which may increase risk of having infections) and thrombocytopenia (low number of platelets, which may cause bleeding and bruising) have been seen when melphalan is used in combination with other medicines which can affect how your immune system works (such as lenalidomide/thalidomide) and others which can increase the benefits of the treatment with melphalan (such as prednisone/dexamethasone).

If you are not sure whether any of the above apply to you, talk to your doctor or pharmacist before using melphalan.

Other medicines and Melphalan

Tell your doctor if you are taking/using, have recently taken/used or might take/use any other medicines.

In particular, tell your doctor or nurse if you are taking/using any of the following:
- other cytotoxic drugs (chemotherapy)
- vaccines which contain live organisms (see "Vaccinations")
- 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 (another chemotherapeutic drug used to treat certain type of cancers)

Vaccinations while you are treated with Melphalan

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

Pregnancy, breast-feeding and fertility

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 this medicine is given.
Do not breast-feed while treated with Melphalan. Ask your doctor for advice.

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.

Fertility/male and female contraception

Do not use Melphalan if you are planning to have a baby. This applies to both men and women. Melphalan may harm your sperm or eggs, 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). 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.
It is recommended that men who are receiving melphalan do not father a child during treatment and up to *3 months* afterwards, therefore reliable contraceptive precautions must be taken during this period.
If you are a women, reliable contraceptive precautions must be taken to avoid pregnancy whilst and up to *6 months* after you are having this treatment.
Ask your doctor for advice.

Driving and using machines

Effects on the ability to drive and operate machinery in patients given this medicine have not been studied. It is not expected that this medicine will affect the ability to drive or operate machines.
The amount of alcohol in this medicinal product may impair your ability to drive or use machines.

Melphalan contains sodium

This medicinal product contains 2.04 mmol (47 mg) sodium per vial of solvent. This is equivalent to 2.4% of the recommended maximum daily dietary intake of sodium for an adult.

Melphalan contains ethanol

This medicinal product contains 5 % ethanol (alcohol), i.e. up to 0.4 g per vial of solvent, equivalent to 10 ml beer, 4.2 ml wine per vial. 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.
The amount of alcohol in this medicinal product may alter the effects of other medicines.
The amount of alcohol in this medicinal product may impair your ability to drive or use machines.

Melphalan contains propylene glycol

This medicine contains 6.3 g propylene glycol in each vial of solvent. Propylene glycol in this medicine can have the same effects as drinking alcohol and increase the likelihood of side effects. If you are pregnant or breast-feeding, do not use this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are using this medicine.
If you suffer from a liver or kidney disease, do not use this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are using this medicine.

3. HOW TO USE MELPHALAN

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

Melphalan is a cytotoxic medicine for use under the direction of physicians experienced in the administration of such medicines.

Melphalan can be given:
- as an infusion into your vein

The following information is intended for healthcare professionals only:

Precautions

Melphalan **is an active cytotoxic agent for use under the direction of physicians experienced in the administration of such agents**. Caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.

Safe handling of Melphalan

The handling of melphalan formulations should follow guidelines for the handling of cytotoxic drugs.

Preparation:

Melphalan powder and solvent for solution for injection/infusion should be prepared at **room temperature** (approximately 25°C), 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. 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.

• as a perfusion to a particular part of your body through an artery.
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 sometimes change your dose as a result of these tests.

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. You will be given the 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.

If you develop any signs or symptoms of thromboembolism (such as shortness of breath, chest pain, arm or leg swelling), tell your doctor immediately. If you experience any thromboembolic events, your doctor may decide to discontinue your treatment and to start a standard anticoagulation therapy. 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.

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.

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

Very common side effects (may affect 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 are given Melphalan directly into your arm or leg.

Common side effects (may affect up to 1 in 10 people):
• Hair loss – with normal 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):
• Dying of muscle tissue (muscle necrosis), muscle decay (rhabdomyolysis) leading to muscle weakness and numbness.
• leukaemia (cancer of the blood).
• in women: your periods stopping (amenorrhoea)
• in men: absence of sperms in the semen (azoospermia)
• Deep vein thrombosis (formation of a blood clot (thrombus) in a deep vein, predominantly in the legs) and pulmonary embolism (a blockage of the pulmonary artery or its branches by a blood clot that breaks loose and migrates into the lungs).
• increased risk of having a second, unrelated cancer in the future.

It is also possible that the use of Melphalan will increase the risk of developing another type of cancer called secondary acute leukaemia (cancer of the blood) in the future. Secondary acute leukaemia causes bone marrow (tissue in your bones that produces red and white blood cells) to produce large numbers of cells that do not work properly. Symptoms of this condition include tiredness, fever, infection and bruising. The condition may also be detected by a blood test which will show if there are large numbers of cells in your blood that are not working properly and too few blood cells that are working properly.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme Website: 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.
Store below 25ºC.
Keep the vial in the outer carton in order to protect from light. Do not refrigerate.
Do not use this medicine after the expiry date, which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.
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.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Melphalan contains
• The active substance is melphalan. Each Melphalan vial contains 50 mg of melphalan (as melphalan hydrochloride).
• The other ingredients are povidone K12 and hydrochloric acid.
Melphalan is dissolved in 10 ml of solvent before being injected. The solvent contains water for injections, sodium citrate dihydrate, propylene glycol and ethanol.

What Melphalan looks like and contents of the pack
Each pack contains one vial of Melphalan white to off-white powder and one vial of clear colourless solvent. The powder vial contains 50 mg of the active substance melphalan in a powder format and the solvent vial contains 10 ml of a solvent in which to reconstitute (dissolve) the powder. When a vial of Melphalan powder is reconstituted with 10 ml of the solvent, the resultant solution contains 5 mg/ml anhydrous melphalan.

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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.

Chemical and physical in-use stability of Melphalan is limited and the solution should be prepared immediately before use. The reconstituted solution (5 mg/ml) should be used immediately and the diluted solution should be completely administrated within 1.5 hour of reconstitution.

Any unused product or waste material should be disposed of in accordance with local requirements.

Administration
Except in cases where regional arterial perfusion is indicated, Melphalan is for intravenous use only.

For intravenous administration it is recommended that Melphalan 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 solution may be administered diluted in an infusion bag.

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 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. For further information, please refer to the Summary of Product Characteristics (SmPC).