Package leaflet: Information for the user

Melphalan medac 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, pharmacist 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, 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 medac is and what it is used for

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

Melphalan medac 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 medac

Do not use Melphalan medac:
- 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, breastfeeding and fertility”).

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

Warnings and precautions
Talk to your doctor or nurse before using Melphalan medac if you:
- have had radiotherapy or chemotherapy, now or recently
- have a kidney problem

- you are going to have a vaccination or were recently vaccinated (see "Having vaccines")
- 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, breastfeeding and fertility).

Melphalan could increase the risk of developing other types of cancer (e.g. 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 if any of the above apply to you, talk to your doctor or pharmacist before using melphalan.

Other medicines and Melphalan medac
Tell your doctor if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor or nurse if you are taking any of the following:
- other cytotoxic medicines (chemotherapy)
- vaccines which contain live organisms (see "Having vaccines")
- 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 medicine used to treat certain types of cancers)

Having vaccines while you are using Melphalan medac
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 medac.

Pregnancy, breastfeeding and fertility
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.
Do not breastfeed while having Melphalan medac. Ask your doctor or midwife for advice.

<u>Pregnancy</u>
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 take 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 6 months afterwards. Reliable contraceptive precautions must be taken to avoid pregnancy whilst you or your partner are having this injection and up to 6 months afterwards. Ask your doctor for advice.

Driving and using machines
Effects on the ability to drive and operate machinery in patients having 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 medicine may impair your ability to drive or use machines.

Melphalan medac contains sodium
This medicine contains 53 mg sodium (main component of cooking/table salt) in each vial of solvent. This is equivalent to 2.7% of the recommended maximum daily dietary intake of sodium for an adult.

Melphalan medac contains ethanol
This medicine contains 0.4 g of alcohol (ethanol) in each vial of solvent which is equivalent to 5% ethanol (alcohol). The amount in one vial of this medicine is equivalent to 10 mL beer or 4.2 mL wine. The amount of alcohol in this medicine is not likely to have an effect in adults and adolescents, but it is likely to affect infants and children, especially aged six or younger. These effects may include feeling sleepy and changes in behaviour. It may also affect their ability to concentrate and take part in physical activities. Talk to your doctor or pharmacist if this medicine is being prescribed for a child suffering from epilepsy or liver problems.
The alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines. If you are pregnant or breast-feeding, talk to your doctor or pharmacist before having this medicine. If you are addicted to alcohol, talk to your doctor or pharmacist before having this medicine.

Melphalan medac contains propylene glycol
This medicine contains 6.00 mL (6,240 mg) 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.
Tell your doctor if you are pregnant, if you have a liver or kidney disease or if you use other medicines containing propylene glycol or alcohol.
Your doctor may carry out extra checks while you are having this medicine.

3. How to use Melphalan medac

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

Melphalan medac is an active cytotoxic agent for use under the direction of physicians experienced in the administration of such agents.

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

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

If you are given more Melphalan medac than you need
Your doctor will give you Melphalan medac 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 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 (rare), 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 (very common) 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 and/or platelets are being produced (very common).
- 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 medac directly into your arm or leg (rhabdomyolysis; not known).
- if you **suddenly** feel unwell (even with a normal temperature).

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

Very common: may affect more than 1 in 10 people
- feeling sick (nausea), being sick (vomiting) and diarrhoea
- mouth ulcers - with high doses of Melphalan medac
- hair loss - with high doses of Melphalan medac
- a tingling or warm feeling where Melphalan medac was injected
- problems with your muscles like wasting and aching - when you are given Melphalan medac directly into your arm or leg.

Common: may affect up to 1 in 10 people
- hair loss - with usual doses of Melphalan medac
- 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 medac directly into your arm or leg.

Rare: 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 medac
- 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 and pulmonary embolism
- increased risk of having a second, unrelated cancer in the future

It is also possible that the use of Melphalan medac 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 HPRA Pharmacovigilance, Website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Melphalan medac

Keep this medicine out of the sight and reach of children.

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 medac 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 medac contains

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

What Melphalan medac looks like and contents of the pack

Each pack contains one vial of Melphalan medac powder and one vial of 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 medac powder is reconstituted with 10 mL of the solvent, the resultant solution contains 5 mg/mL anhydrous melphalan.

Marketing Authorisation Holder and Manufacturer

medac Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany
Tel.: +49 4103 8006-0
Fax: +49 4103 8006-100

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria, Czech Republic, Denmark, Finland, Germany, Hungary, Ireland, Norway, Poland, Sweden: Melphalan medac
France: MELPHALAN MEDAC
Italy, Netherlands: Melfalan medac
Portugal: Melfalano medac
Spain: Melfalán medac
United Kingdom (Northern Ireland): Melphalan

This leaflet was last revised in 01/2022.

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

Preparation
Melphalan medac solution for injection/infusion should be prepared, **at room temperature** (approximately 25 °C), by reconstituting the freeze-dried powder with the solvent 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 at least 120 seconds) until a clear colourless to clear light brown colour solution without visible particles, is obtained. Each vial must be reconstituted individually in this manner. The resulting solution contains the equivalent of 5 mg/mL melphalan.

Melphalan medac is not compatible with infusion solutions containing dextrose, and it is recommended that **only** sodium chloride intravenous infusion 0.9% w/v is used.

Chemical and physical in-use stability of Melphalan medac is limited and the solution should be prepared immediately before use. The reconstituted solution (5 mg/mL) should be transferred into the infusion bag in less than 30 minutes and the diluted solution should be completely administrated within 1.5 hour of reconstitution.

The reconstituted solution is clear colourless to clear light brown colour solution and practically free from visible particles, with a final pH of approximately 6.5.

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 medac is for intravenous use only.

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

Care should be taken to avoid possible extravasation of Melphalan medac and in cases of poor peripheral venous access, consideration should be given to use of a central venous line. If high-dose Melphalan medac 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 (SPC).