PACKAGE LEAFLET

Package leaflet: Information for the user

Melphalan 50 mg powder and solvent for solution for injection/infusion

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.
- If you get any side effects, talk to your doctor or pharmacist. 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 are given Melphalan
3. How Melphalan will be given
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 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.

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 the 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 breast-feeding.

If you are not sure, talk to your doctor or nurse before melphalan is given.

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 Mephalan
- 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 your arteries
- 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.

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.

Men who are receiving melphalan should not father a child during treatment and up to 3 months afterwards.

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

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. This includes herbal medicines.

In particular, tell your doctor or nurse if you are taking any of the following:

- other cytotoxic medicines (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, 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.

Pregnancy

Treatment with melphalan is not recommended during pregnancy because it may cause permanent damage to a foetus. Do not take melphalan if you are planning to have a baby. This applies to both men and women. Reliable 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 being given melphalan. Your doctor will consider the risks and benefits to you and your baby of treatment with melphalan.

Breast-feeding

It is unknown whether melphalan is excreted in human breast milk. Do not breast-feed 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

Women of childbearing potential should use effective contraceptive measures during treatment with melphalan and for 6 months after the end of treatment.

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 or 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 53.5 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 2.7% of the recommended maximum daily dietary intake of sodium for an adult.

Melphalan contains ethanol

This medicinal product contains 5% ethanol (alcohol) respectively 0.4 g per vial equivalent to 10 ml beer or 4 ml wine per vial.

Harmful for those suffering from alcoholism.

To be taken into account in pregnant 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 6.2 g propylene glycol in each vial.

Propylene glycol in this medicine can have the same effects as drinking alcohol and increase the likelihood of side effects.

Do not use this medicine in children less than 5 years old.

Use this medicine only if recommended by a doctor. If you suffer from a liver or kidney disease, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are taking this medicine.

3. How Melphalan will be given

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

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

<u>Method of administration:</u>

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 medicines 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)
- treatment with melphalan can cause a lowering of the white blood cell count. White blood cells fight infection, and when there are too few white blood cells, infections can occur

- 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

- if you experience any of the symptoms/signs which may be related to a blood clot (thromboembolic event) such as shortness of breath, chest pain, arm or leg swelling, especially if you are treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone.

If melphalan is injected directly into your arm or leg it is possible that some of the drug can leak in to surrounding tissue and cause damage to that tissue. Symptoms of this include slight discomfort in the area, mild redness of the skin or a mild rash. In rare cases death of surrounding skin tissue, ulcers and damage to deeper tissue may occur.

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 fall in the number of blood cells and platelets
- feeling sick (nausea), being sick (vomiting) and diarrhoea, - with high doses of melphalan
- 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
- Inflammation of the soft tissue lining of the stomach (gastrointestinal mucosa).

Unommon side effects (may affect up to 1 in 100 people):

- acute kidney injury.

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 fibres (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).

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

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.

Tell your doctor as soon as possible if you have any of these symptoms. You may need to stop taking melphalan, but only your doctor can tell you if that is the case.

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 pack carton after 'Exp'. The expiry date refers to the last day of that month.

This medicinal product does not require any special temperature storage conditions. Keep the vial in the outer carton, in order to protect from light.

Melphalan will be prepared for use by a healthcare professional. Once prepared it should be used immediately. Any unused product or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Melphalan contains

The active substance is melphalan. Each vial contains 50 mg of melphalan.

The other ingredients are:

Vial with powder: povidone K12 and hydrochloric acid, dilute.

Vial with solvent: water for injections, sodium citrate dihydrate, propylene glycol and ethanol.

Melphalan is dissolved in a diluent before being injected.

What Melphalan looks like and contents of the pack

Each pack contains one melphalan vial and one solvent vial.

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.

Powder: Clear type I moulded glass vial sealed with omniflex 3G coated bromobutyl rubber stopper and flip off aluminium seal having orange colour polypropylene button with matte finish. Vials may or may not be sleeved with shrink sleeves. Pack size: 1 vial containing 50 mg melphalan.

Solvent: Clear type I moulded glass vial sealed with bromobutyl rubber stopper and flip off aluminium seal having orange colour polypropylene button with matte finish.

Pack size: 1 vial containing 10 ml.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Tillomed Laboratories Ltd
220 Butterfield, Great Marlings
Luton
LU2 8DL
United Kingdom

Manufacturer[1]

MIAS Pharma Limited
Suite 2, Stafford House
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Co. Dublin, Ireland

Tillomed Malta Limited
Malta Life Sciences Park
LS2.01.06 Industrial Estate
San Gwann, SGN 3000
Malta

[1]Only the actual release site will be listed on the marketed product

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The following information is intended for healthcare professionals only:

Procedures for proper handling and disposal of cytotoxic medicinal products should be observed:

1. The personnel are to be instructed in the reconstitution of the medicinal product.
2. Pregnant women should be excluded from handling this medicine.
3. The personnel should wear suitable protective clothing with face masks, safety goggles and gloves when reconstituting the preparation.
4. Any items used for administration or cleaning, including gloves, should be disposed of in waste containers for contaminated material to high-temperature combustion. Liquid waste can be discharged with plenty of water.

In case of accidental eye contact with melphalan, immediately rinse with sodium chloride eyewash or plenty of water and immediately consult a doctor. In case of skin contact, immediately wash the affected areas with soap and plenty of cold water and consult a doctor immediately. The spilled solution should be immediately wiped with a damp paper towel, which must then be disposed of safely. The contaminated surfaces must be washed with plenty of water.

Reconstitution

Melphalan should be prepared at room temperature (approximately 25°C), by reconstituting the powder with the solvent-diluent provided.

It is important that both the powder and the solvent provided are at room temperature (approximately 25°C) before starting reconstitution.

10 ml of the solvent should be added quickly as a single quantity into the vial containing the powder, using a sterile needle and syringe. A 21 gauge or higher gauge needle should be used for piercing of vial stopper during reconstitution. For smooth and effective penetration, the needle should be inserted perpendicularly into the stopper, not too fast or too rough without twisting. . Immediately shake the vial vigorously (for approximately 5 minutes) until a clear solution, without visible particles, is obtained. Rapid addition of diluent followed by immediate vigorous shaking is important for proper dissolution.

Shaking of the formulation leads to a significant amount of very small air bubbles. These bubbles can remain for 2 to 3 minutes as the resulting solution is quite viscous. This can make it difficult to assess the clarity of the solution.

Each vial must be reconstituted individually in this manner. The resulting solution contains the equivalent of 5 mg per ml anhydrous melphalan. Failure to follow above mentioned preparation steps may result in incomplete dissolution of melphalan.

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

Take 10 ml of above reconstituted solution having concentration of 5 mg/ml of anhydrous melphalan into infusion bag containing 100 ml of 0.9% Sodium chloride injection. Mix this diluted solution thoroughly 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**

room temperature of approximately 25°C, the maximum time from preparation of the 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 9 mg/ml (0.9%) solution for injection 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 1.5 hours should be discarded according to standard guidelines for handling and disposal of cytotoxic medicinal products.

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