**PACKAGE LEAFLET**

**Package Leaflet: Information for the user**

**Alkeran 50mg Powder and Solvent for Solution for Infusion**
melphalan

**Read all of this leaflet carefully before you are given 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 Alkeran is and what it is used for

Alkeran 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.

Alkeran 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 (stage 4)** - (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 Alkeran is given

**You will not be given Alkeran 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 Alkeran is given.

**Warnings and precautions**

Talk to your doctor or nurse before using Alkeran, 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 Alkeran.
- 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.
- 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).
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Alkeran 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 Alkeran.

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

**Other medicines and Alkeran**

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 (another chemotherapeutic drug used to treat certain type of cancer)s)

**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 this medicine is given.

Treatment with Alkeran is not recommended during pregnancy because it may cause permanent damage to a foetus. Do not take Alkeran 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.

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.

If you are already pregnant, it is important to talk to your doctor before being given Alkeran. Your doctor will consider the risks and benefits to you and your baby of taking Alkeran.

Do not breast-feed while being given Alkeran. Ask your doctor for advice.

**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). 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.

Alkeran contains 53.24 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to approximately 2.6% of the recommended maximum daily dietary intake of sodium for an adult.

Alkeran contains 416 mg of alcohol (ethanol) in each vial, which is equivalent to 41.6mg/ml (4% w/v). The amount in each vial of this medicine is equivalent to less than 11 ml beer or 5 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

Alkeran contains 6048 mg propylene glycol in each vial, which is equivalent to 604.8 mg/ml.

If your child is less than 5 years old, talk to your doctor or pharmacist before giving them this medicine, in particular if they use other medicines that contain propylene glycol or alcohol.

If you are pregnant or breast-feeding, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are taking this medicine.

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 Alkeran is given

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

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

Alkeran 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 Alkeran you will be given. The amount of Alkeran 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 Alkeran, 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***
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).

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.

***Neutropenia and thrombocytopenia***
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).

**Use in Children**
Alkeran is only rarely indicated in children. Dosing guidelines for children are not available.

**If you are given more Alkeran than you need**
Your doctor will give you Alkeran 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 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 a high temperature or infection (sore throat, sore mouth or urinary problems).
- Treatment with Alkeran 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 have Alkeran directly into your arm or leg.
- If Alkeran is injected directly in to 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.
- If you experience any of the symptoms/signs which may be related to a thromboembolic event (such as shortness of breath, chest pain, arm or leg swelling) especially if you are treated with Alkeran in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone.

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- with high doses of Alkeran
- mouth ulcers - with high doses of Alkeran
- hair loss - with high doses of Alkeran
- a tingling or warm feeling where Alkeran was injected
- problems with your muscles like wasting and aching - when you are given Alkeran directly into your arm or leg.

**Common (affects less than 1 in 10 people)**
- hair loss - with usual doses of Alkeran
- 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 Alkeran 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 Alkeran
- 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)
- breakdown of muscle fibers (rhabdomyolysis)
- deep vein thrombosis and pulmonary embolism
- acute kidney injury – kidney failure (significant reduction of kidney function) that happens within a short time.
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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 Alkeran 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 Alkeran, 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 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 Alkeran

- Keep this medicine out of the sight and reach of children.
- Do not use Alkeran after the expiry date, which is stated on the vials and carton after 'Exp'. This is printed as month; year and refers to the last date of the month
- Do not store Alkeran Injection above 30°C. Do not refrigerate. Keep the vials in the outer carton, to protect from light.
- Your Alkeran 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 Alkeran contains**
The active substance is melphalan. Each Alkeran injection contains 50 mg of melphalan.
The other ingredients are povidone K12 and hydrochloric acid. Alkeran is dissolved in 10 ml of solvent before being injected. The solvent contains water for injections, sodium citrate, propylene glycol and ethanol.
This medicinal product contains small amounts of ethanol less than 100 mg per dose.
It also contains 53.24 mg of sodium per vial of reconstituted product, which should be taken into account by patients on a controlled sodium diet.

**What Alkeran looks like and contents of the pack**
Each pack contains one vial of Alkeran 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 Alkeran powder is reconstituted with 10 ml of the solvent, the resultant solution contains 5 mg/ml anhydrous melphalan.

**Marketing Authorisation Holder and Manufacturer**
Marketing Authorisation holder: Aspen Pharma Trading Limited, 3016 Lake Drive, Citywest Business Campus, Dublin 24, Ireland
Tel: +353 1 6 308 400

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

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**Information for Healthcare Professionals**

*For further information please refer to the Summary of Product Characteristics (SPC)*

**Instructions for Use and Handling**

***Safe Handling of Alkeran Injection:***

Alkeran Injection should be prepared for administration either by or under the direct supervision of a pharmacist who is familiar with its properties and safe handling requirements.
Refer to local cytotoxic guidelines before commencing.
Alkeran Injection 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 Alkeran Injection 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 Alkeran Injection 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 eyewash 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 are trying to conceive should not handle Alkeran injection. .

***Disposal:***

Alkeran Injection solution should be disposed of in compliance with relevant local legislation. In the absence of such guidelines, the solution should be disposed of in a manner appropriate for toxic chemicals, for example, high-temperature incineration or deep burial.
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.
All disposals must be in accordance with local regulatory requirements.

***Preparation of Alkeran Injection Solution:***

(see also above, Safe Handling of Alkeran).
Alkeran Injection should be prepared, AT ROOM TEMPERATURE, by reconstituting the freeze-dried powder with the solvent provided.
If the solvent is used at cold temperature, the freeze-dried powder may not reconstitute properly and undissolved particles may be observed.
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 50 seconds) until a clear colourless solution without visible particles, is obtained. Each vial must be reconstituted individually in this manner. Slow solvent addition and delaying the shaking may lead to the formation of insoluble particles. It should also be noted that the shaking process creates a considerable amount of very small

air bubbles. These bubbles may persist and may take a further 2 to 3 minutes to clear, as the resulting solution is quite viscous.
The resulting solution contains the equivalent of 5 mg/ml anhydrous melphalan and has a pH of approximately 6.5.
The reconstituted solution should be colourless, clear and practically free from visible particles.
Alkeran Injection solution has limited stability and should be prepared immediately before use. Any unused solution remaining after one hour should be discarded (see Disposal, above).
The reconstituted solution should not be refrigerated, as this will cause precipitation.
When further diluted in an infusion solution, Alkeran 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 hour.
Alkeran Injection is not compatible with infusion solutions containing dextrose and it is recommended that ONLY Sodium Chloride Intravenous Infusion 0.9% w/v is used. (Please refer to section 4.2 of the SmPC).
Should any visible turbidity or crystallisation appear in the reconstituted or diluted solutions the preparation must be discarded.

**For instructions on administration of Alkeran please refer to the SPC.**
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