Package Leaflet: Information for the User

Alkeran® 2 mg Film-Coated Tablets

melphalan

Read all of this leaflet carefully before you start taking 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 tablets contain 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 tablet 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 **breast cancer.**
- **Polycythaemia rubra vera -** a type of blood cancer where the number of red cells in your blood increases due to uncontrolled red blood cell production in your body. This makes the blood thicken and causes blood clots, and may result in headaches, dizziness and shortness of breath.

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 take Alkeran

Do not take 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 pharmacist before taking Alkeran.

Warnings and precautions

Before you take Alkeran, tell your doctor or nurse 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 taking melphalan.
- 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.

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

Please tell your doctor if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription. This includes herbal medicines.

In particular, you must tell your doctor 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 cancers).

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 taking this medicine.

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 contraceptive precautions must be taken to avoid pregnancy whilst you or your partner is taking these tablets.
If you are already pregnant, it is important to talk to your doctor before taking Alkeran.
Your doctor will consider the risks and benefits to you and your baby of taking Alkeran.

Do not breast-feed during treatment with 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. It is recommended that men who are receiving treatment with melphalan not father a child during treatment and up to 6 months afterwards.

Driving and using machines

Effects on the ability to drive and operate machinery in patients taking this medicine have not been studied.

3. How to take Alkeran

Alkeran should only be given to 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.

Always take Alkeran exactly as your doctor has told you. It is important to take your medicine at the right times. The label on your pack will tell you how many tablets to take and how often to take them. If the label doesn't say or if you are not sure, ask your doctor, nurse or pharmacist.

- Swallow your tablets whole with a glass of water.
- **Do not break, crush or chew the tablets.**

The dose of Alkeran depends on the type of your blood problem or cancer (see section 1).

Your doctor may also change your dose during your treatment, depending on your needs. The dose can sometimes be changed if you are an older person or have a kidney problem.
When you take 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.

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

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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).

Multiple myeloma
- The usual dose is 0.15 mg per kilogram of your body weight each day for 4 days. This is repeated every 6 weeks.

Advanced ovarian adenocarcinoma
- The usual dose is 0.2 mg per kilogram of your body weight each day for 5 days. This is repeated every 4 to 8 weeks.

Advanced breast carcinoma
- The usual dose is 0.15 mg per kilogram of your body weight each day for 5 days. This is repeated every 6 weeks.

Polycythaemia rubra vera
- Initially 6 to 10 mg each day for 5 to 7 days. The dose will then be reduced to 2 to 4 mg each day.

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

If you take more Alkeran than you should
If you take more Alkeran than you should, tell your doctor immediately or go to a hospital straight away. Take the medicine pack with you.

If you forget to take Alkeran
Tell your doctor. **Do not take a double dose to make up for a forgotten dose.**

If you stop taking Alkeran
If you have any further questions on the use of this medicine, ask 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 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

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

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 sperm in the semen (azoospermia)
- deep vein thrombosis and 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 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.

5. How to store Alkeran

- 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 bottle label and the carton after 'Exp'. This is printed as month; year and refers to the last date of the month.
- Store in a refrigerator between 2 and 8°C.
- If your doctor tells you to stop taking the tablets, it is important to return any which are left over to your pharmacist, who will destroy them according to disposal of dangerous substance guidelines. Only keep the tablets if your doctor tells you to.
- 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 Alkeran contains
The active substance is melphalan. Each Alkeran tablet contains 2 mg of melphalan. The other ingredients are microcrystalline cellulose, crospovidone, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide (E171) and macrogol.

What Alkeran looks like and contents of the pack
Alkeran tablets are white to off-white film-coated, round, biconvex tablets engraved with 'GX EH3' on one side and 'A' on the other. Your Alkeran tablets are in bottles of 25 tablets.

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Marketing Authorisation holder:
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