Package leaflet: Information for the user

Mifamurtide 4 mg powder for concentrate for dispersion for infusion
mifamurtide

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.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Mifamurtide is and what it is used for

Mifamurtide contains the active substance mifamurtide, similar to a component of the cell wall of certain bacteria. It stimulates your immune system to help your body kill tumour cells.

Mifamurtide is used to treat osteosarcoma (bone cancer) in children, adolescents and young adults (between 2 and 30 years). It is used after you have had surgery to remove the tumour and together with chemotherapy to kill remaining cancer cells to reduce the risk of cancer coming back.

2. What you need to know before you use Mifamurtide

Do not use Mifamurtide:
- if you are allergic to mifamurtide or any of the other ingredients of this medicine (listed in section 6).
- if you are taking medicines containing ciclosporin or other calcineurin inhibitors or high doses of non-steroidal-anti-inflammatory drugs (NSAIDs) (see “Using other medicines” below).

Warnings and precautions
Talk to your doctor before using Mifamurtide:
- if you have or have had problems with your heart or blood vessels, like blood clots (thrombosis), bleeding (haemorrhage) or inflammation of the veins (vasculitis). You should be more closely monitored while receiving Mifamurtide treatment. If you have long-lasting or worsening symptoms, you should contact your doctor, as Mifamurtide treatment may need to be delayed or discontinued.
- if you have a history of asthma or other breathing disorders. Before using Mifamurtide, you should discuss with your doctor whether you should take medicine for your asthma when using Mifamurtide.
- if you have a history of inflammatory or autoimmune disease or have been treated with corticosteroids or other medicines that may affect your immune system.
- if you have any allergic reactions to any medicines such as rash, breathlessness and high blood pressure. If you have worsening symptoms, you should contact your doctor, as these may have been caused by Mifamurtide.

- if you have stomach problems such as nausea, vomiting and lack of appetite. If your problems increase, you should contact your doctor, as these may have been caused by Mifamurtide when used with chemotherapy.
- if you develop chills or shivering, or feel warm. You should take your temperature as you may have a fever. A fever with a low white blood cell count (neutropenia) may be a sign of serious infection.

Detailed information on warnings and precautions relating to side effects that could occur while you are taking the medicine is presented in section 4.

Children
It is not recommended to give this medicine to children below the age of 2 years because information on how safe and how well this medicine works is not available for this age group.

Other medicines and Mifamurtide
Tell your doctor if you are taking, have recently taken or might take any other medicines. This includes medicines that may be obtained without a prescription. It is especially important to tell your doctor if you are taking medicines containing any of the following active substances:

- ciclosporin, tacrolimus, used after a transplant to prevent rejection of transplanted organs, or other immunosuppressants used e.g. to treat psoriasis (a skin disease).
- Non-steroidal-anti-inflammatory drugs (NSAIDs), such as acetylsalicylic acid, ibuprofen, or diclofenac, used for treatment of headaches, fever or pain. You must not use Mifamurtide with high doses of NSAIDs.
- corticosteroids, used to treat inflammations, allergies or asthma. Regular use of corticosteroids should be avoided when using Mifamurtide as this may affect the way the medicine works.

It is recommended to separate the times of administration of Mifamurtide and doxorubicin or other medicines if used in the same chemotherapy treatment regimen.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or planning to have a baby, ask your doctor for advice before taking this medicine.
Mifamurtide has not been tested in pregnant women. Therefore, Mifamurtide should not be used during pregnancy and in women of childbearing potential not using effective contraception.
You should use effective contraception if you are being treated with Mifamurtide.

It is not known whether Mifamurtide passes to human milk. If you are breast-feeding, you should discuss with your doctor.

Driving and using machines
Some very common and common side effects of Mifamurtide treatment (such as dizziness, vertigo, fatigue and blurred vision) may affect your ability to drive and use machines.

Mifamurtide contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’.

3. How to use Mifamurtide

Dose and duration of treatment
Mifamurtide will be administered only under the supervision of a specialist physician.
Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose of Mifamurtide is 2 mg mifamurtide/m^2 body surface area. It will be given to you twice a week (at least three days apart) for the first 12 weeks, then once a week for 24 more weeks.

The schedule of your Mifamurtide treatments can be adjusted to fit with your chemotherapy schedule. It is not necessary to interrupt your schedule of Mifamurtide if your chemotherapy is delayed; you should complete 36 weeks (9 months) of treatment with Mifamurtide without an interruption.

How Mifamurtide is given
The freeze-dried powder has to be reconstituted into a liquid suspension, filtered using the filter provided and further diluted before use. Mifamurtide is then infused directly into your vein (intravenous) over about 1 hour. This is done by your doctor or a nurse, who will also monitor you during that time. You do not need to be hospitalised to receive Mifamurtide. It can also be administered as an outpatient.

If you use more Mifamurtide than you should
You may experience more severe side effects, including fever, chills, fatigue, nausea, vomiting, headache and high blood pressure or low blood pressure. In the event of such an overdose, contact your doctor or nearest hospital.

If you stop using Mifamurtide
You should not stop treatment with Mifamurtide before finishing the course of treatment without discussing with your doctor first. If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, Mifamurtide can cause side effects, although not everybody gets them.

The majority of patients experience chills, fever and fatigue especially during the first administration of Mifamurtide. These are typically mild to moderate and transient and can usually be treated by your doctor, e.g. with paracetamol for fever.
Treatment with Mifamurtide can often cause stomach problems such as nausea, vomiting and loss of appetite when used with chemotherapy.

Contact your doctor **immediately**:
- if you have continuing fever or chills more than 8 hours after your dose of Mifamurtide, because this may be a sign of an infection, or
- if you experience rash or have any problems breathing (wheezing), or
- if you experience any stomach problems.

Very common side effects (may affect more than 1 in 10 people):
- fever, shaking/shivering, weakness, tiredness or general discomfort
- nausea and/or vomiting, diarrhoea or constipation
- headache or dizziness
- rapid beating of the heart
- high blood pressure or low blood pressure
- no appetite for food
- sweating
- pain, including general pain, pain in your muscles and/or joints and pain in back, chest, abdomen, arm or leg
- cough, trouble breathing or rapid breathing
- low body temperature
- low number of red blood cells

Common side effects (may affect up to 1 in 10 people):
- blue colour of tissues such as the skin or gums caused by too little oxygen
- perceptible increase in frequency or force of heartbeat
- swelling in arms or legs or other swelling
- chest discomfort
- upset stomach, decreased appetite or weight loss
- injection site or catheter site redness, swelling, infection or other local reaction
- rash or redness, inflammation of the skin, itching, dry skin, pale or transient red appearance
- inflammation of skin, tendons, muscles or similar tissues that support body structure
- inflammation of a vein
- upper abdominal or chest wall pain; abdominal bloating or pain; indigestion or pain in your liver
- other pain, including neck, shoulder, groin, bone or throat pain; pain after an operation
- muscle spasms or stiffness
- feeling cold
- tired feeling, drowsiness or sleepiness
- burning, pricking/tingling sensation, diminished sensitivity to sensation or feeling a sensation without stimulus
- involuntary shaking movement
- dehydration
- low concentration of potassium in blood
- mucosal inflammation
- nose, throat, or sinus congestion or inflammation
- infections of the upper respiratory tract (such as a cold) or the urinary tract (such as a bladder infection)
- generalised infection
- *Herpes simplex* (virus) infection
- productive cough, wheezing or exertional or exacerbated shortness of breath
- spitting of blood or nosebleed
- fluid in the lung cavity
- blood in urine, difficulty or pain in urination or frequent urination
- difficulty sleeping, depression, anxiety or confusion
- dizziness
- ears ringing
- blurred vision
- hair loss
- difficult, painful menstruation
- hearing loss
- low number of white blood cells with or without fever, low number of platelets

Not known (cannot be estimated from the available data):
- abnormal accumulation of fluid around the heart (pericardial effusion)

Reporting of side effects
If you get any side effects talk to your doctor. This includes any side effects not listed in this leaflet. You can also report side effects directly via the 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 Mifamurtide

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 vial label and the carton after "EXP". The expiry date refers to the last day of that month.

Unopened vial
Store in a refrigerator (2 °C-8 °C). Do not freeze.
Keep the vial in outer carton in order to protect from light.

Reconstituted suspension
Once reconstituted in sodium chloride 9 mg/mL (0.9%) solution, store at room temperature (approximately 20ºC - 25ºC) and use within 6 hours.
Do not use this medicine if you notice any visible signs of deterioration.
Do not throw away any medicines via wastewater. These measures will help protect the environment.

6. Contents of the pack and other information

What Mifamurtide contains
- The active substance is mifamurtide. Each vial contains 4 mg of mifamurtide. After reconstitution, each mL of suspension contains 0.08 mg of mifamurtide.
- The other ingredients are 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) and 1,2-Dioleoyl-sn-glycero-3-phospho-L-serine monosodium salt (OOPS). See section 2 "Mifamurtide contains sodium"

What Mifamurtide looks like and contents of the pack
Mifamurtide is a white to off-white homogeneous cake or powder for concentrate for dispersion for infusion.

Mifamurtide is supplied in a carton that contains
- One 50 mL vial with a grey butyl stopper, aluminium seal and plastic flip-off cap.
- One sterile filter for Mifamurtide supplied in a blister.

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The following information is intended for healthcare professionals only:

Instructions for preparation of Mifamurtide for intravenous infusion

Materials provided in each package -
- 1 vial of Mifamurtide (mifamurtide)
- 1 Filter for Mifamurtide

Materials required but not provided -

- Sodium chloride 9 mg/mL (0.9%) solution for injection, 100 mL bag
- 1 single use 60 or 100 mL sterile syringe with luer lock
- 2 medium (18) gauge sterile injection needles

It is recommended that the reconstitution of the liposomal suspension should be performed in a laminar flow cabinet utilising sterile gloves using aseptic technique.

The lyophilised powder should be allowed to reach a temperature between approximately 20 °C-25 °C prior to reconstitution, filtering using the filter provided and dilution. This should take approximately 30 minutes.

1. The cap of the vial should be removed and the stopper cleaned using an alcohol pad.
2. The filter should be removed from the blister pack, and the cap removed from the filter spike.
   The spike should then be inserted into the vial septum firmly until seated. The filter luer connector cap should not be removed at this time.
3. The 100 mL sodium chloride 9 mg/mL (0.9%) solution for injection bag, needle and syringe should be unpacked (not provided in the pack).
4. The site of the sodium chloride 9 mg/mL (0.9%) solution for injection bag where the needle is going to be inserted should be swabbed with an alcohol pad.
5. Using the needle and syringe, 50 mL of sodium chloride 9 mg/mL (0.9%) solution for injection should be withdrawn from the bag.
6. After removing the needle from the syringe, the syringe should be attached to the filter by opening the filter luer connector cap (figure 1).

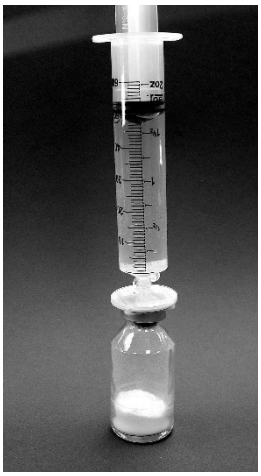

Figure 1

7. The sodium chloride 9 mg/mL (0.9%) solution for injection is added to the vial by slow, firm depression of the syringe plunger. **The filter and syringe must not be removed from the vial.**
8. The vial should be allowed to stand undisturbed for 1 minute to ensure thorough hydration of the dry substance.
9. **The vial should then be shaken vigorously for 1 minute while keeping the filter and syringe attached.** During this time the liposomes are formed spontaneously (figure 2).

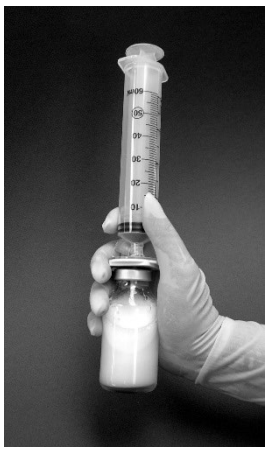

Figure 2

10. The desired dose may be withdrawn from the vial by inverting the vial and slowly pulling back on the syringe plunger (figure 3). Each mL reconstituted suspension contains 0.08 mg mifamurtide. The volume of suspension to be withdrawn for dose quantities is calculated as follows:

    Volume to withdraw = [12.5 x calculated dose (mg)] mL

    For convenience, the following table of concordance is provided:

Dose	Volume
1.0 mg	12.5 mL
2.0 mg	25 mL
3.0 mg	37.5 mL
4.0 mg	50 mL

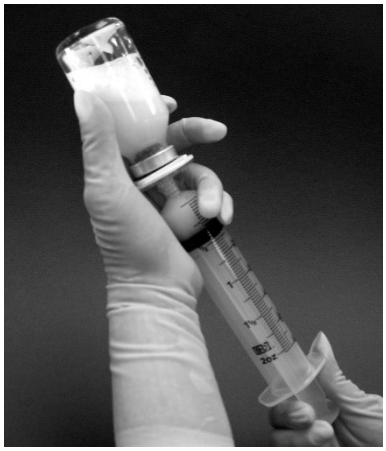

Figure 3

11. The syringe should then be removed from the filter and a new needle placed on the suspension-filled syringe. The bag injection site should be wiped with an alcohol pad and the suspension in the syringe should be injected into the original bag containing the remaining 50 mL of sodium chloride 9 mg/mL (0.9%) solution for injection (figure 4).

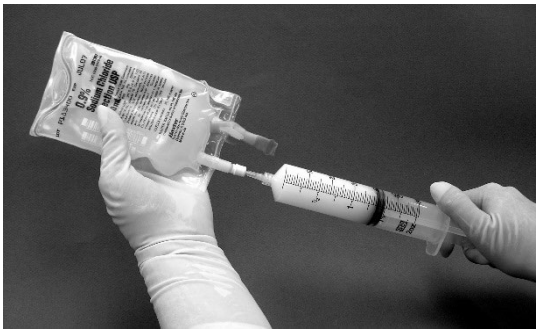

Figure 4

12. The bag should be gently swirled to mix the solution.
13. Patient identification, time and date should be added to the label on the bag containing the reconstituted, filtered and diluted liposomal suspension.
14. Chemical and physical in-use stability has been demonstrated for 6 hours at room temperature (between approximately 20 °C-25 °C).
15. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at room temperature.

No special requirements for disposal.