Package leaflet: Information for the user
Arsenic Trioxide Phebra
1 mg/ml concentrate for solution for infusion

arsenic trioxide

PilNJ208.3

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 further questions, please ask your doctor or your 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 or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Arsenic Trioxide Phebra is and what it is used for

Arsenic Trioxide Phebra is used to treat a type of leukaemia called 'Acute Promyelocytic Leukaemia' or 'APL'. This is a type of myeloid leukaemia – a disease with abnormal white blood cells and abnormal bleeding and bruising.

Arsenic Trioxide Phebra is used in adult patients with:

- newly diagnosed low-to-intermediate risk APL
- those whose leukaemia has not responded to other therapies.

2. What you need to know before you use Arsenic Trioxide Phebra

Do not use Arsenic Trioxide Phebra if:

- you are allergic to arsenic trioxide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Arsenic Trioxide Phebra, if:

- you have reduced kidney function
- you have any liver problems

If any of the above apply to you, or you are not sure, talk to your doctor, pharmacist or nurse before using Arsenic Trioxide Phebra.

Tests and checks

Your doctor will do the following tests and checks:

- Blood tests to check the amount of potassium, magnesium, calcium and creatinine in your blood before your first dose of Arsenic Trioxide Phebra.
- Blood tests on your potassium, calcium and liver function should be repeated during your treatment with this medicine.
- An ECG (an electrical recording of the heart) before your first dose – and then twice a week when you are using the medicine.
- If you are at risk for a certain type of abnormal heart beat (such as 'torsade de pointes' or 'QTc prolongation'), your heart will be monitored throughout your treatment.
- Your doctor may monitor your health during and after treatment since arsenic trioxide, the active substance in this medicine, may cause other cancers. Report any new and unusual side effects whenever you see your doctor.
- Follow-up of your cognitive and mobility functions if you are at risk for vitamin B1 deficiency.

Children and adolescents

Arsenic Trioxide Phebra is not recommended in children and young people below 18 years of age.

Other medicines and Arsenic Trioxide Phebra

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines- including medicines obtained without a prescription and herbal medicines.

In particular tell your doctor or pharmacist if you are taking, have recently taken, or might take any medicines listed below:

- any medicine which may affect your liver – if you are not sure, show the medicine bottle or pack to your doctor.
- medicine which could change how your heart beats – as the effects of these medicines on your heartbeat can be made worse by Arsenic Trioxide Phebra. These include:
  - medicines to treat serious mental health problems (such as thioridazine)
  - medicines for depression (such as amitriptyline)
  - some types of medicines used to correct uneven heartbeats (such as quinidine, amiodarone, sotalol, dofetilide)
  - some antibiotics to treat bacterial infections (such as erythromycin and sparfloxacin)
  - some anti-histamines to treat allergies such as hay fever (such as terfenadine and astemizole)
  - medicines that can decrease the magnesium or potassium in your blood (such as amphotericin B)
  - cisapride (a medicine for certain stomach problems).

Arsenic Trioxide Phebra with food and drink

There are no restrictions on your food or drink while you are receiving Arsenic Trioxide Phebra.

Pregnancy and contraception information for women and men

Ask your doctor or pharmacist for advice before using this medicine.
Arsenic Trioxide Phebra may cause harm to the unborn baby when used by pregnant women.

If you are pregnant, or you become pregnant during treatment with this medicine, you must ask your doctor for advice. If you are able to become pregnant, you must use effective contraception during treatment with Arsenic Trioxide Phebra.

Men must use effective contraception while being treated with Arsenic Trioxide Phebra.

Breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Do not breast-feed during treatment with this medicine. This is because the arsenic in Arsenic Trioxide Phebra passes into breast milk and can harm your baby.

Driving and using machines

Arsenic Trioxide Phebra should have no or very little effect on your ability to drive and use machines. If you have discomfort or if you feel unwell after an Arsenic Trioxide Phebra injection - wait until the signs go away before driving or using machines.

Arsenic Trioxide Phebra contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 10 ml, that is to say essentially 'sodium-free'.

3. How to use Arsenic Trioxide Phebra

Arsenic Trioxide Phebra is normally given by a doctor or a nurse. It must be given under the supervision of a doctor experienced in the treatment of acute leukaemias.

How Arsenic Trioxide Phebra is given

It is given as a drip (infusion) into a vein over 1-2 hours. The infusion may last longer if you get side effects such as flushing and feeling dizzy.

Patients with newly diagnosed APL

- In your first treatment cycle, your doctor will give you:
  - one dose every day as a drip (infusion).
  - you may be treated every day up to 60 days - or until your doctor decides that your leukaemia is improving.
- If your leukaemia responds to Arsenic Trioxide Phebra, you will be given 4 more treatment cycles of:
  - one dose given every day for 5 days (followed by 2 days break) for 4 weeks
  - this will be followed by a 4 week break.

Your doctor will then decide exactly how long you must continue using Arsenic Trioxide Phebra.

Patients with APL, whose leukaemia has not responded to other therapies

- In your first treatment cycle, your doctor will give you:
  - one dose every day as a drip (infusion).
  - you may be treated every day up to 50 days - or until your doctor decides that your leukaemia is improving.
- If your leukaemia responds to Arsenic Trioxide Phebra, you will be given a second treatment cycle of:
  - one dose given every day for 5 days (followed by 2 days break) for 5 weeks.

Your doctor will then decide exactly how long you must continue using Arsenic Trioxide Phebra.

If your doctor gives you more Arsenic Trioxide Phebra than they should

If you have more of this medicine than you should, you may have fits, muscle weakness and confusion. If you notice these signs, tell your doctor straight away who will stop treatment with Arsenic Trioxide Phebra. The doctor may also treat you for an arsenic overdose.

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.

The following side effects may happen with this medicine:

Serious side effects

Tell your doctor or nurse straight away if you notice any of the following serious side effects:

These may be signs of a severe problem called 'differentiation syndrome', which might be fatal:

- difficulty breathing
- coughing
- chest pain
- fever

These may be signs of severe allergic reaction:

- difficulty breathing
- fever
- sudden weight gain
- water retention
- fainting
- palpitations (strong heartbeat you can feel in your chest)

Other side effects:

While on treatment with this medicine, you may experience some of the following reactions:

Very common (may affect more than 1 in 10 people):

- fatigue (weariness), pain, fever, headache
- nausea, vomiting, diarrhoea
- feeling dizziness, muscle pain, numbness or tingling
- rash or itching
- increased blood sugar
- oedema (swelling due to excess fluid)
- feeling short of breath, fast heartbeat, abnormal ECG
- abnormal blood results – shown in tests: reduced potassium or magnesium, abnormal liver function tests including excess bilirubin or 'gamma-glutamyltransferase'

Common (may affect up to 1 in 10 people):

- reduction in blood cell counts (platelets, red or white blood cells), increased white blood cells
- chills
- increased weight
- a fever due to an infection and low levels of white blood cells
- herpes zoster infection
- chest pain
- bleeding in the lung
- low oxygen levels (hypoxia)
- collection of fluid around the heart or the lung
- low blood pressure
- abnormal heart beat
- fit (seizures)
- joint or bone pain, inflammation of the blood vessels
- stomach (abdominal) ache
- redness of the skin, swollen face, blurred vision
- abnormal blood results – shown in tests: increased sodium or magnesium, ketones in the blood and urine (ketoacidosis), abnormal renal function tests, kidney failure

Not known (it is not known how often these happen):

- lung infection, infection in the blood
- inflammation of the lungs - which causes chest pain and breathlessness, cardiac failure
- dehydration, confusion
- cerebral disease (encephalopathy, Wernicke encephalopathy) with various manifestations including difficulties to use arms and legs, speech disorders and confusion

Tell your doctor, pharmacist or nurse if you get any of the side effects listed above.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist or nurse.

This includes any possible 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 Arsenic Trioxide Phebra

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. The expiry date refers to the last day of that month.

Do not freeze.

After dilution, if not used immediately, storage times and conditions before use are the responsibility of your doctor and would normally not be longer than 24 hours at 2– 8ºC, unless dilution has taken place in a sterile environment.

From a microbiological point of view, the product must be used immediately.

This medicine is a clear, colourless solution. Do not use this medicine if you notice flakes or particles, or if the solution is discoloured.

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 to protect the environment.

6. Contents of the pack and other information

What Arsenic Trioxide Phebra contains

- The active substance is arsenic trioxide. Each 1 ml of concentrate contains 1 mg of arsenic trioxide.
- The other ingredients are sodium hydroxide, hydrochloric acid (for pH adjustment) and water for injections

What Arsenic Trioxide Phebra looks like and contents of the pack

- Arsenic Trioxide Phebra is a concentrate for solution for infusion.
- Arsenic Trioxide Phebra is supplied in glass vials as a concentrated, sterile, clear, colourless, particle-free aqueous solution that is prepared and diluted at the hospital, and given as an infusion into a blood vessel.
- Each carton contains 10 single-use glass vials. Each 10 ml vial contains 10 mg of arsenic trioxide.

Marketing Authorisation Holder

Phebra Limited
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Manufacturer

Flexipharm Austrading Limited
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Detailed information on this medicine is available on the Medicines and Healthcare products Regulatory Agency web site: http://www.mhra.gov.uk

Information on medicines containing the same active substance and for the same disease is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

There are also links to other websites about rare diseases and treatments.

The following information is intended for medical or healthcare professionals only:

ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT HANDLING OF ARSENIC TRIOXIDE PHEBRA SINCE NO PRESERVATIVE IS PRESENT.

Dilution of Arsenic Trioxide Phebra

Arsenic Trioxide Phebra must be diluted before administration.

Personnel should be trained to handle and dilute arsenic trioxide and should wear appropriate protective clothing.

Carefully insert the needle of a syringe into the vial and draw up all of the content. Arsenic Trioxide Phebra must then be diluted immediately with 100 to 250 ml of glucose 50 mg/ml (5%) solution for injection or sodium chloride 9 mg/ml (0.9%) solution for injection.

Unused portions of each vial must be discarded properly. Do not save any unused portions for later administration.

Use of Arsenic Trioxide Phebra

For single use only. Arsenic Trioxide Phebra must not be mixed with or concomitantly administered in the same intravenous line with other medicinal products.

Arsenic Trioxide Phebra must be administered intravenously over 1-2 hours. The infusion duration may be extended up to 4 hours if vasomotor reactions are observed. A central venous catheter is not required.

The diluted solution must be clear and colourless. All parenteral solutions must be inspected visually for particulate matter and discoloration prior to administration. Do not use the preparation if foreign particulate matter is present.

After dilution in intravenous solutions, Arsenic Trioxide Phebra is chemically and physically stable for 48 hours at 15-30°C and 72 hours at refrigerated (2-8°C) temperatures. From a microbiological point of view, the product must 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 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Procedure for proper disposal

Any unused product, any items that come into contact with the product, and waste material must be disposed of in accordance with local requirements.