

**Package leaflet: Information for the user**  
**Arsenic trioxide 1 mg/ml concentrate for solution for infusion**  
Arsenic trioxide

**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 further questions, please ask your doctor, pharmacist, or nurse.
- 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 is and what it is used for
2. What you need to know before you are given Arsenic Trioxide
3. How Arsenic Trioxide is given
4. Possible side effects
5. How to store Arsenic Trioxide
6. Contents of the pack and other information

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

Arsenic Trioxide contains the active ingredient arsenic trioxide which belongs to a group of medicines called antineoplastics.

It is used in adult patients:

- newly diagnosed with low-to-intermediate risk acute promyelocytic leukemia (APL),
- whose disease has not responded to other therapies.

APL is a unique type of myeloid leukemia, a disease in which abnormal white blood cells and abnormal bleeding and bruising occur.

**2. What you need to know before you are given Arsenic trioxide**

Arsenic Trioxide must be given under the supervision of a physician experienced in the treatment of acute leukemias.

**You must not receive Arsenic Trioxide**

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

**Warnings and precautions**

You must talk to your doctor or nurse before you are given Arsenic trioxide, if

- you have impaired kidney function.
- you have any liver problems.

Your doctor will take the following precautions:

- Tests will be performed to check the amount of potassium, magnesium, calcium, and creatinine in your blood before your first dose of arsenic trioxide.
- You should have an electrical recording of the heart (electrocardiogram ECG) performed before your first dose.
- Blood tests (potassium, calcium, magnesium, and liver function) should be repeated during your treatment with arsenic trioxide.
- In addition, you will receive electrocardiograms (ECG) once or twice weekly.
- If you are at risk for a certain type of abnormal heart rhythm (e.g., torsade de pointes or QTc prolongation), your heart will be monitored continuously.
- Your doctor may monitor your health during and after treatment, since arsenic trioxide, the active substance in Arsenic Trioxide, may cause other cancers. You should report any new and exceptional symptoms and circumstances whenever you see your doctor.
- Follow-up of your cognitive and mobility functions if you are at risk for vitamin B1 deficiency.
- Your doctor will perform a pregnancy test if you are at childbearing age.

**Children and adolescents**

Arsenic trioxide is not recommended in children and adolescents below 18 years of age.

### **Other medicines and Arsenic Trioxide**

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

In particular tell your doctor:

- if you are taking any of various types of medicines which could cause a change in the rhythm of your heartbeat. These include:
  - some types of antiarrhythmics (medicines used to correct irregular heartbeats, e.g., quinidine, amiodarone, sotalol, dofetilide)
  - medicines to treat psychosis (loss of contact with reality, e.g., thioridazine)
  - medicines for depression (e.g., amitriptyline)
  - some types of medicines to treat bacterial infections (e.g., erythromycin and sparfloxacin)
  - some medicines to treat allergies such as hay fever, called antihistamines (e.g., terfenadine and astemizole)
  - any medicines that cause a decrease in magnesium or potassium in your blood (e.g., amphotericin B, diuretics)
  - cisapride (a medicine used to relieve certain stomach problems).

The effect of these medicines on your heartbeat can be made worse by arsenic trioxide. You must be sure to tell your doctor about all medicines you are taking.

- if you are taking or have recently taken any medicine which may affect your liver. If you are not sure, show the bottle or pack to your doctor.
- ziprasidone or pimozide; medicines used to treat psychosis; arsenic trioxide should not be used concomitantly with these 2 medications because of potential additive adverse effects on the heartbeats (prolongation of the QT intervals).

### **Arsenic trioxide with food and drink**

There are no restrictions on your food or drink while you are receiving arsenic trioxide.

### **Pregnancy**

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

Arsenic trioxide may cause harm to the fetus when used by pregnant women.

If you are able to become pregnant, you must use effective birth control during treatment with Arsenic trioxide and for 6 months following completion of treatment. Your doctor will undertake a pregnancy test for you if you are at childbearing age (see section warnings and precautions above)

If you are pregnant or you become pregnant during the treatment with Arsenic trioxide, you must ask your doctor for advice.

Men should also use effective contraception and be advised to not father a child while receiving Arsenic trioxide and for 3 months following completion of treatment.

### **Breast-feeding**

Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether arsenic and/or its metabolites are excreted in milk. Because arsenic trioxide can harm nursing infants, do not breast-feed while on and until two weeks after the last dose of arsenic trioxide.

### **Driving and using machines**

Arsenic trioxide is expected to have no or negligible influence on your ability to drive and use machines. If you experience discomfort or if you feel unwell after receiving arsenic trioxide injection, you should wait until the symptoms go away before driving or using machines.

### **Arsenic Trioxide contains sodium**

This medicine contains less than 1 mmol sodium (23 mg) per dose. This means that the medicine is essentially “sodium-free”.

## **3. How Arsenic Trioxide is given**

### **Duration and frequency of treatment**

#### Patients with newly diagnosed acute promyelocytic leukemia

Your doctor will give you arsenic trioxide once every day as an infusion among other medications. In your first treatment cycle, you may be treated every day for up to 60 days at most or until your doctor determines that your disease is better (induction phase). If your disease responds to arsenic trioxide, you will be given 4 additional treatment cycles. Each cycle consists of 20 doses given 5 days per week (followed by 2 days interruption) for 4 weeks followed by 4

weeks interruption (consolidation phase). Your doctor will decide exactly how long you must continue on therapy with arsenic trioxide.

Patients with acute promyelocytic leukemia, whose disease has not responded to other therapies

Your doctor will give you arsenic trioxide once every day as an infusion. In your first treatment cycle, you may be treated every day up to 50 days at most or until your doctor determines that your disease is better (induction phase). If your disease responds to arsenic trioxide, you will be given a second treatment cycle of 25 doses given 5 days per week (followed by 2 days interruption) for 5 weeks (consolidation phase). Your doctor will decide exactly how long you must continue on therapy with arsenic trioxide.

**Method and route of administration**

Arsenic trioxide must be diluted with a solution containing glucose or a solution containing sodium chloride.

Arsenic trioxide is normally given by a doctor or a nurse. It is given as a drip (infusion) into a vein over 1-2 hours, but the infusion may last longer if side effects like flushing and dizziness occur.

Arsenic trioxide must not be mixed with or infused through the same tube with other medicines.

**If your doctor or nurse gives you more arsenic trioxide than he/she should**

You may experience convulsions, muscle weakness and confusion. If this happens, treatment with arsenic trioxide must be stopped immediately and your doctor will treat the arsenic overdose.

If you have any further question on the use of this medicine, ask your doctor, pharmacist, or nurse.

**4. Possible side effects**

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

**Tell your doctor or nurse straight away if you notice the following side effects, as these may be signs of a severe condition called “differentiation syndrome”, which might be fatal:**

- difficulty in breathing and/or weight gain
- coughing

- chest pain
- fever

**Tell your doctor or nurse straight away if you notice one or more of the following side effects, as these may be signs of allergic reaction:**

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

While on treatment with arsenic trioxide, you may experience some of the following reactions:

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

- Fever
- Liver injury
- Irregular heartbeat including fast heartbeats originating from the lower chambers of the heart, premature ventricular contractions, QTc-prolongation
- Increase in the number of white blood cells, decrease in the number of one type of white blood cells called neutrophils (neutropenia), decrease in the number of platelets (thrombocytopenia)
- Infection

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

- Fatigue, APL differentiation syndrome
- Nausea, vomiting, diarrhea, abdominal pain, mucositis
- Cough, sore throat, dyspnea, pleuritic pain
- Headache, insomnia, peripheral neuropathy, paresthesia, mood alteration, musculoskeletal pain, seizures

- reduced potassium or magnesium in the blood, abnormal liver function tests including presence of excess bilirubin or gamma-glutamyl transferase in the blood
- torsade de pointes, ventricular tachycardia
- Febrile neutropenia, hemorrhage, thrombosis
- Rash, Pruritus
- Bone pain, arthralgia, musculoskeletal pain
- ECG: QT prolongation, Liver function test show increase in ALT, increase in aspartate amino transferase

**Uncommon (may affect up to 1 in 100 people):**

- Chest pain, pain
- Pulmonary alveolar hemorrhage (bleeding from many alveoli throughout the lungs.), pleural effusion (accumulation of water on the lungs), hypoxia
- Hypermagnesemia, hypernatremia, ketoacidosis
- Cerebral vascular accident - CVA (obstruction in blood flow to the brain), collection of fluid around the heart
- leucopenia vasculitis (small blood vessel inflammation)
- Renal failure
- Dermatitis, erythema
- Increase bilirubin level, hypomagnesaemia

**Rare (may affect up to 1 in 1000 people):**

- Immune suppression causing herpes zoster

**Reporting of side effects**

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via National Pharmacovigilance and Drug Safety Centre (NPC), SFDA. By reporting side effects, you can help provide more information on the safety of this medicine.

## **5. How to store Arsenic Trioxide**

- 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. This medicine does not require any special storage conditions.
- After first opening: Once opened the product should be used immediately.
- Shelf life after dilution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C and for 7 days at 2°C to 8°C. From a microbiological point of view, the product must be used immediately after dilution. 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°C-8°C, see Dilution of Arsenic trioxide below.
- This medicine must not be used if you notice foreign particulate matter or if the solution is discolored.
- 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 does Arsenic Trioxide contain**

The active substance is arsenic trioxide. One mL of concentrate contains 1 mg arsenic trioxide.

One vial contains 10 mg of arsenic trioxide in 0ml.

The other ingredients are: sodium hydroxide, concentrated hydrochloric acid (for pH adjustment) and water for injections. See section 2, “Arsenic trioxide contains sodium”.

### **What Arsenic Trioxide looks like and contents of the pack**

Arsenic Trioxide is a concentrate for solution for infusion. Arsenic Trioxide is a concentrated, sterile, clear, colorless, aqueous solution supplied in clear glass vials with rubber stoppers and an aluminum seal with a plastic flip-off cap.

Supplied in cartons of 10.

**Marketing Authorization Holder**

International Pioneers Pharmaceuticals

3225 Ibn Hubairah St. Malaz Area,

Riyadh,

KSA

**Manufacturer**

Oncomed Manufacturing A.S

Karasek 2229/1b , 62100 Brno - Czech Republic

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Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>

**To report any side effect(s):**

- Saudi Arabia:

The National Pharmacovigilance Centre (NPC):

Fax: +966-11-205-7662

SFDA Call Center: 19999

E-mail: [npc.drug@sfda.gov.sa](mailto:npc.drug@sfda.gov.sa)

Website: <https://ade.sfda.gov.sa>

- Other GCC States:

Please contact the relevant competent authority.

### **This is a Medicament**

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

Council of Arab Health Ministers

Union of Arab Pharmacists

### **The following information is intended for healthcare professionals only:**

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

#### **Dilution of Arsenic Trioxide**

- Arsenic trioxide must be diluted before administration.
- PVC-free plastic bags should be used.
- Personnel should be trained to handle and dilute arsenic trioxide and should wear appropriate protective clothing.
- Dilution: Carefully insert the needle of a syringe into the vial through the rubber stopper and draw up all of the content. Arsenic trioxide 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**

- For single use only. Arsenic trioxide must not be mixed with or concomitantly administered in the same intravenous line with other medicinal products.
- Arsenic trioxide 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 colorless. 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 is chemically and physically stable for 24 hours at 25°C and for 7 days under refrigeration (2-8°C). 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.

**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.