Package leaflet: Information for the user

Cytarabine and associated names 100 mg/ml solution for injection or infusion
Cytarabine

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

What is in this leaflet:

1. What Cytarabine is and what it is used for

- Cytarabine is used in adults and children.
- This medicine contains cytarabine, which is one of a group of medicines known as cytotoxics. These medicines are used in the treatment of acute leukaemias (cancer of blood where you have too many white blood cells). Cytarabine interferes with the growth of cancer cells, which are eventually destroyed.
- Cytarabine is also used for the induction and maintenance of remission of leukaemia.
- Remission induction is an intensive treatment to force leukaemia into retreat. When it works, the balance of cells in your blood becomes more normal and your health improves. This relatively healthy period is called a remission.
- Maintenance therapy is a milder treatment to make your remission last as long as possible. Quite low doses of cytarabine are used to keep the leukaemia under control and stop it flaring up again.

2. What you need to know before you are given Cytarabine

Do not use cytarabine if you:
- are allergic to cytarabine, or any of the other ingredients of this medicine (listed in section 6).
- if your blood cell count (number of cells in your blood) is very low due to some cause other than cancer. Your doctor might not give this medicine if you have a non-malignant disease, except for immunosuppression.
- if you have had severe effects on your brain (encephalopathy) after radiation treatment or treatment with another anticancer medicine such as methotrexate

Warnings and precautions
Take special care with Cytarabine

- if your bone marrow is in low state, therapy should be initiated under close medical supervision.
- your liver and kidney function should be monitored during cytarabine therapy. If your liver is not working well before treatment, cytarabine should be given only under strict control.
- you have had or are due to have any vaccination including a live or live-attenuated vaccination.
- cytarabine strongly reduce blood cell production in the bone marrow. This can make you more prone to infection or bleeding. The blood cell numbers can continue to fall for up to a week after stopping treatment. Your doctor will test your blood regularly and examine your bone marrow if required.
- serious and sometimes life-threatening side effects can occur in the central nervous system, the bowels or lungs.
- the levels of uric acid (showing that the cancer cells are destroyed) in your blood (hyperuricaemia) may be high during treatment. Your doctor will tell you if you need to take any medicine to control this.

Other medicines and Cytarabine
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.
- given medicines containing 5-Fluorocytosine (a medicine used to treat fungal infections).
- taking medicines containing digitoxin or beta-acetyldigoxin which are used to treat certain heart conditions.
- taking gentamicin (an antibiotic used to treat bacterial infections).
- given medicines containing cyclophosphamide, vincristine and prednisone which are used in cancer treatment programmes.
- you are given cytarabine in combination with methotrexate administered through your spine, because cases of headache, paralysis, coma and stroke-like symptoms have been reported in children and young adults given intravenous Cytarabine in combination with intrathecal methotrexate.

Pregnancy and breast-feeding

Pregnancy
Avoid becoming pregnant while you or your partner is being treated with cytarabine. If you are sexually active, you are advised to use effective birth control to prevent pregnancy during treatment, whether you are male or female. Cytarabine may cause birth defects, so it is important to tell your doctor if you think you are pregnant**.** Men and women have to use effective contraception during and up to 6 months after treatment.

Breast-feeding
You should stop breast-feeding before starting treatment with cytarabine because this medicine may be harmful to infants being breast-fed.

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

Driving and using machines
If you feel unwell following treatment with Cytarabine you should avoid driving or using machinery.

Important information about some of the ingredients of cytarabine

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

3. How Cytarabine is given to you

Cytarabine will be given to you by infusion into a vein (through a 'drip') or by injection under the direction of specialists in hospital. Your doctor will decide what dose to give and the number of days' treatment you will receive depending on your condition.

Based on your condition, your doctor will decide the dose of cytarabine, whether you are in induction or maintenance therapy and your body surface area. Your body weight and height will be used to calculate your body surface area.

Regular Check-ups
During treatment you will need regular checks including blood tests. Your doctor will tell you how often this should be done. He/she will be making regular checks of:

- Your blood- to check for low blood cell counts that may need treatment.
- Your liver– using blood tests – to check that cytarabine is not affecting the way it functions in a harmful way.
- Your kidneys– using blood tests – to check that cytarabine is not affecting the way it functions in a harmful way.
- Blood uric acid levels - cytarabine may increase uric acid levels in the blood. Another medicine may be given if your uric acid levels are too high.

If you receive high doses of cytarabine:
High doses can worsen side effects like sores in the mouth or may decrease the number of white blood cells and platelets (these help the blood to clot) in the blood. Should this happen, you may need antibiotics or blood transfusions. Mouth ulcers can be treated to make them less uncomfortable as they heal.

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

4. Possible side effects

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

Tell your doctor or nurse immediately, if you suffer from the following symptoms after being given this medicine:

- An allergic reaction such as sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips, rash or itching (especially affecting the whole body).
- You are feeling tired and lethargic.
- You have flu like symptoms e.g. raised temperature or fever and chills.
- You bruise more easily or bleed more than usual if you hurt yourself. These are the symptoms of **low numbers of blood cells.**

Other side effects that may occur are:
If any of these side effects gets serious please **tell your doctor or nurse immediately.**

Very common: may affect more than 1 in 10 people

- Pneumonia, infection (which can become serious and lead to organ failure),
- Insufficient production or decrease in numbers of red blood cells, white blood cells or platelets.
- Inflammation or appearance of sores in the mouth, lips, or on the anus , feeling sick, being sick, diarrhoea, abdominal pain
- Liver damage (seen in blood test)
- Hair loss is common and may be quite severe. Hair normally re-grows when your treatment course ends.
- Skin rash
- Cytarabine syndrome, sometimes the following side effects can happen together 6 to12 hours after receiving Cytarabine. Feeling generally unwell with a high temperature, pain in bone, muscle and sometimes the chest, blistery rash, sore eyes. This is called "Cytarabine Syndrome" and can be treated.
- Feeling hot and feverish
- Abnormal bone marrow results from a biopsy, or blood results from a smear test

Common: may affect up to 1 in 10 people
- Ulceration on your skin
- Abnormal high blood uric acid levels
- Swallowing difficulty

Uncommon: may affect up to 1 in 100 people
- Presence of gaseous cysts in the intestinal wall
- Severe bowel inflammation
- Serious infection of the membrane that lines the abdomen

Very rare: may affect up to 1 in 10,000 people
- Irregular heart beat
- Inflammation of sweat glands

Not known: frequency cannot be estimated from the available data
- You may get an infection, including infection or inflammation at the site of your injection
- Loss of appetite
- Headaches or feeling dizzy, feeling of pins and needles, shaking and fits, drowsiness, sore or itchy eyes
- Pericarditis (inflammation of the covering of the heart)
- Slower than usual heart rate or heart beat
- Inflammation to your veins (caused by a blood clot)
- Shortness of breath, sore throat, pain or difficulty swallowing
- Pancreatitis (pain in the upper abdomen) often accompanied by feeling sick or vomiting, inflammation or ulcers in the gullet, causing heartburn may make you feel sick,
- Jaundice (seen as yellowing of the skin and whites of the eye)
- Skin redness (similar to sunburn), pain and numbness in joints, fingers, toes or face, swelling of the abdomen, legs, ankles and feet, a sensation of tingling or burning, tenderness and tightness of the skin, thick calluses on the palms and hands, itchy skin rash, itching or increased freckles
- Difficulty or pain when passing urine. Blood in your urine and impaired kidney function (seen in blood test)

The following side effects have been reported with high dose therapy:

Very common: may affect more than 1 in 10 people

- Affected alertness speech problems, involuntary muscle movement or difficulty coordinating muscle movement, involuntary eye movements, headache, confusion, somnolence, dizziness, etc. caused by brain disorder.
- Eye infection, irritation, pain and blurred vision, visual loss
- Short or stabbing chest pain, build up of fluid in the lungs

Common: may affect up to 1 in 10 people

- Peeling of the skin
- Infection and inflammation of the intestines, most common in babies

Not known: Frequency cannot be estimated from the available data

- A pus-filled mass inside the liver & enlarged liver
- Changes in your personality
- Coma, convulsions, poor balance caused by damage to nerves
- Fast heart beat, reduced function of the heart, shortness of breath, dizziness, swelling of legs, ankles, feet and veins in the neck (cardiomyopathy), which can be fatal
- Blood in vomiting or in stools (gastrointestinal necrosis or ulcer), stomach pain or tenderness (peritonitis), blood clot within the hepatic veins (Budd–Chiari syndrome)
- Muscle injury (rhabdomyolysis), absence of menstrual periods in a woman during her reproductive years (amenorrhoea), men who don't have sperm in their semen (azoospermia).

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 United Kingdom Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard.

Ireland
HPRA Pharmacovigilance
Earlsford Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: + 353 1 676 2517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cytarabine

Keep out of the sight and reach of children.

Store between 15°C to 25°C. Do not refrigerate or freeze.

Do not use cytarabine injection after the expiry date which is stated on the vial or carton. The expiry date refers to the last day of that month. The product should be used immediately after opening the vial.

After dilution in the following diluents, sterile water for injections, glucose intravenous infusion (5 % w/v) or sodium chloride intravenous infusion (0.9 % w/v):

Chemical and physical in-use stability has been demonstrated for 8 days below 25 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions 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.

Do not use cytarabine injection if you notice that the solution is not clear, colourless and free of particles.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Cytarabine contains:

The active ingredient is cytarabine.

Each ml of solution contains 100 mg of cytarabine.

Each 1 ml vial contains 100 mg of cytarabine.
Each 5 ml vial contains 500 mg of cytarabine.
Each 10 ml vial contains 1 g of cytarabine.
Each 20 ml vial contains 2 g of cytarabine.

The other ingredients are hydrochloric acid, sodium hydroxide and water for injections.

What Cytarabine looks like and contents of the pack

The medicinal product is presented as a clear, colourless solution for injection or infusion. This medicine is presented in a clear colourless, type I glass vials with bromobutyl rubber stopper and sealed with flip-off aluminium overseal green (2 ml), blue (5 ml), red (10 ml) and yellow (20 ml).

The package contains 1 vial of 1 ml, 5 ml, 10 ml and 20 ml, respectively.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

For UK:
Fresenius Kabi Oncology Plc

Lion Court, Farnham Road Bordon, Hampshire,
GU35 0NF United Kingdom

For IRL
Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

Manufacturer:
Fresenius Kabi Deutschland GmbH
Pfingstweide 53
61169 Friedberg
Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

Czech Republic	Cytarabin Kabi 100 mg/ml, Injekční a infuzní roztok
Denmark	Cytarabin Fresenius Kabi
Estonia	Cytarabine Kabi
Spain	Citarabina 100 mg/ml solución inyectable o para perfusión
France	Cytarabine Kabi 100 mg/ml, solution injectable ou pour perfusion
Hungary	Cytarabine Kabi 100 mg/ml oldatos injekció vagy infúzió
Ireland	Cytarabine 100 mg/ml Solution for Injection or Infusion
Iceland	Cytarabin Fresenius Kabi 100 mg/ml stungulyf/innrennslislyf, lausn
Latvia	Cytarabine Kabi 100 mg/ml šķīdums injekcijām vai infūzijām
Lithuania	Cytarabine Kabi 100 mg/ml injekcinis/ infuzinis tirpalas
Netherlands	Cytarabine Fresenius Kabi 100 mg/ml Oplossing voor injectie of infusie
Norway	Cytarabin "Fresenius Kabi" 100 mg/ml Injeksjons-/infusjonsvæske, oppløsning
Poland	Cytarabine Kabi
Portugal	Citarabina Kabi
Romania	Citarabina Kabi 100 mg/ml soluţie injectabilă sau perfuzabilă
Sweden	Cytarabin Fresenius Kabi 100 mg/ml injektions-/infusionsvätska, lösning
Slovak Republic	Cytarabin Kabi 100 mg/ml, injekčný a infúzny roztok,
United Kingdom	Cytarabine 100 mg/ml Solution for Injection or Infusion

This leaflet was last approved in

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

Instruction for Use/Handling

For single use only.

Cytarabine is intended for intravenous or subcutaneous use only.

The diluted solution should be clear, colourless solution free, from visible particles.

Parenteral drugs should be inspected visually for particulate matter and discolouration, prior to administration, whenever solution and container permit.

If the solution appears discoloured or contains visible particles, it should be discarded.

Cytarabine injection can be diluted with sterile water for injections, glucose intravenous infusion (5 % w/v) or sodium chloride intravenous infusion (0.9 % w/v).

The dilution compatibility study has been carried out in polyolefin infusion bags.

The concentration over which the physico-chemical stability of cytarabine has been demonstrated is 0.04 - 4 mg/ml.

If crystallization is observed as a result of exposure to low temperatures, redissolve the crystals by warming up to 55°C for no longer than 30 minutes and shake until the crystals are dissolved. Allow to cool to room temperature before use.

Once opened, the contents of each vial must be used immediately and not stored.

Infusion fluids containing cytarabine should be used immediately.

<u>Cytotoxic Handling Guidelines</u>
Administration:

Should be administered by, or under the direct supervision of, a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

Preparation (Guidelines):
1. Chemotherapeutic agents should be prepared for administration only by professionals trained in the safe use of the preparation.
2. Operations such as dilution and transfer to syringes should be carried out only in the designated area.
3. The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.
4. Pregnant personnel are advised not to handle chemotherapeutic agents.

Contamination:
(a) In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat the transient stinging of skin. Medical advice should be sought if the eyes are affected.

(b) In the event of spillage, operators should put on gloves and mop up the spilled material with a sponge kept in the area for that purpose. Rinse the area twice with water. Put all solutions and sponges into a plastic bag and seal it.

Disposal:

Syringes, container, absorbent materials, solution and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated at 1100^{o}C.

Any unused product or waste material should be disposed of in accordance with local requirements.