Package leaflet: Information for the user

Cytarabine 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 or pharmacist or nurse
- This medicine has been prescribed for you. 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 of the 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 Cytarabine injection is and what it is used for

- Cytarabine injection is used in adults and children. The active ingredient is cytarabine.
- Cytarabine is one of a group of the 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.
- 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 spell 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 use Cytarabine injection

Do not use Cytarabine injection
- If you are allergic (hypersensitive) to cytarabine, or any of the ingredients of Cytarabine Injection.
- If the cell count in your blood report is very low due to some cause other than cancer, or as decided by your doctor.
- If you are feeling increasing difficulties in body coordination after radiation treatment with another anticancer drug such as methotrexate.

Warnings and precautions
Talk to your doctor or pharmacist or nurse before using Cytarabine injection Take special care with Cytarabine Injection:
- If your bone marrow is in low state, therapy should be initiated under close medical supervision.
- If you have problems with your liver.
- Cytarabine strongly reduces blood cell production in the bone marrow. This can make you more prone to infections 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
- Your liver and kidney functions should be monitored during cytarabine therapy. If your liver is not working well before treatment, cytarabine should be given only with utmost care.
- 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.
- During treatment with cytarabine administration of live or attenuated vaccine is not advised. If required, consult your doctor. Use of killed or inactivated vaccine may not have the desired effect due to suppressed immune system while on cytarabine.
- Do not forget to tell you doctor if you have received radiotherapy.

Other medicines and Cytarabine injection
Tell your doctor or pharmacist if you are taking, have recently taken or might take 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.

Pregnancy, breast-feeding and fertility
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.

Fertility
Cytarabine may lead to suppression of menstrual cycles in females and lead to amenorrhoea and may suppress sperm production in male patients. Male patients undergoing cytarabine treatment should use a reliable contraceptive method.

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

Driving and using machines
Cytarabine does not affect your ability to drive or use machinery. However, cancer treatment in general can affect the ability of some patients to drive or operate machines. If you are affected, you should not drive or use machinery.

3. How to use Cytarabine injection

Method and routes of administrations
Cytarabine will be given to you by infusion into a vein (through a 'drip') or by injection into a vein or by subcutaneous 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.

The recommended dose is
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.

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 – again using blood tests – to check that Cytarabine is not affecting the way it functions in a harmful way.
- Your kidneys – again 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 are on dialysis, the doctor may alter the time of drug administration as dialysis may decrease the effectiveness of the medicine.

If you take more Cytarabine injection than you should
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 or pharmacist.

4. Possible side effects

Like all medicines, Cytarabine injection can cause side effects, although not everybody gets them.
The side effects of cytarabine are dependent on the dose. The digestive tract is most commonly affected, but also the blood.

Tell your doctor or nursing staff who will be monitoring you during this time immediately, if you suffer from the following symptoms after taking 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).
- severe allergic reaction (anaphylaxis): skin rash including red itchy skin, swelling of the hands, feet, ankles, face, lips mouth or throat (which may cause difficulty in swallowing or breathing) bronchospasm and you may feel you are going to faint (a spontaneous loss of consciousness caused by insufficient blood to the brain). It may be fatal *(uncommon).*
- Clinical signs as present in pulmonary oedema/ARDS may develop, particularly in high-dose therapy: acute, distressing breathing difficulties and water in the lungs (pulmonary oedema) have been observed, particularly at high doses *(common).*
- You are feeling tired and lethargic.
- You have flu like symptoms e.g. raised temperature or fever and chills.
- Severe pain in the chest
- Severe pain in the abdomen
- Loss of vision, loss of sense of touch, mental disturbance or loss of ability to move normally (this medicine may cause side effects to the brain and eyes which are usually reversible but may be very serious)
- You bruise more easily or bleed more than usual if you hurt yourself. These are the symptoms of **low numbers of blood cells. Tell your doctor or nursing staff immediately** if you experience these symptoms.

These are serious side effects. You may need urgent medical attention.
Common (affects 1 to 10 users in 100):
- Fever
- Not enough white and red blood cells or blood platelets, which may make you more prone to infections or bleeding
- a fall in white blood cells can be accompanied by chills and fever that immediately require a medical opinion;
- A fall in the platelet count can be accompanied by bleeding that immediately require a medical opinion,
- Abnormal blood cells (megaloblastosis)
- Loss of appetite
- Swallowing difficulty
- Belly ache (abdominal pain)
- Nausea (feeling sick)
- Vomiting
- Diarrhoea
- Inflammation or ulceration of the mouth or anus
- Reversible effects on the skin such as reddening (erythema), blistering, rash, hives, blood vessel inflammation (vasculitis), hair loss
- Reversible effects on the liver such as increased enzyme levels
- Reversible effects on the eyes such as sore eyes with bleeding (haemorrhagic conjunctivitis) with vision disturbance, sensitivity to light (photophobia), watery or burning eyes and inflammation of the cornea (keratitis)
- Reduced consciousness (at high doses)
- Speaking difficulties (at high doses)
- Abnormal eye movements (nystagmus at high dose)
- Inflammation of the vein at the site of injection
- Abnormally high blood uric acid levels (hyperuricaemia)

Uncommon (affects 1 to 10 users in 1,000):
- Sore throat
- Headache
- Serious allergic reactions (anaphylaxis), causing for instance difficulty in breathing or dizziness
- Blood-poisoning (sepsis)

The following information is intended for medical or healthcare professionals only

Posology and method of administration
By intravenous infusion or injection, or subcutaneous injection.
Cytarabine 100 mg/ml should not be administered by the intrathecal route.
Dosage recommendations may be converted from those in terms of bodyweight (mg/kg) to those related to surface area (mg/m^2) by means of nomograms.

1. Remission induction:
a) Continuous treatment:
i) Rapid injection - 2 mg/kg/day is a judicious starting dose. Administer for 10 days. Obtain daily blood counts. If no antileukaemic effect is noted and there is no apparent toxicity, increase to 4 mg/kg/day and maintain until therapeutic response or toxicity is evident. Almost all patients can be carried to toxicity with these doses.
ii) 0.5 - 1.0 mg/kg/day may be given in an infusion of up to 24 hours duration. Results from one-hour infusions have been satisfactory in the majority of patients. After 10 days this initial daily dose may be increased to 2 mg/kg/day subject to toxicity. Continue to toxicity or until remission occurs.
b) Intermittent treatment:
3-5 mg/kg/day are administered intravenously on each of five consecutive days. After a two to nine-day rest period, a further course is given. Continue until response or toxicity occurs.
The first evidence of marrow improvement has been reported to occur 7 - 64 days (mean 28 days) after the beginning of therapy.
In general, if a patient shows neither toxicity nor remission after a fair trial, the cautious administration of higher doses is warranted. As a rule, patients have been seen to tolerate higher doses when given by rapid intravenous injection as compared with slow infusion. This difference is due to the rapid metabolism of Cytarabine and the consequent short duration of action of the high dose.
ii) Cytarabine 100-200 mg/m^2/24 hours, as continuous infusion for 5-7 days alone or in combination with other cytostatics including for instance an anthracycline has been used. Additional cycles may be administered at intervals of 2-4 weeks, until remission is achieved or unacceptable toxicity occurs

2. Maintenance therapy:
i) Remissions, which have been induced by Cytarabine, or by other drugs, may be maintained by intravenous or subcutaneous injection of 1 mg/kg once or twice weekly.
ii) Cytarabine has also been administered in doses of 100-200 mg/m^2, as continuous infusion for 5 days at monthly intervals as monotherapy or in combination with other cytostatics.
In high dose, Cytarabine, under strict medical surveillance, is administered as monotherapy or in combination with other cytostatics, 2-3 g/m^2, as intravenous infusion, for 1-3 hours every 12 hours for 2-6 days. (Total of 12 doses per cycle). A total treatment dose of 36 g/m^2 should not be exceeded.
Paediatric patients:
Safety in infants has been not established.
Patient with hepatic and renal impairment:
Patient with impaired hepatic or renal function: Dosage should be reduced.
Elderly Patients:
There is no information to suggest that a change in dosage is warranted in the elderly. Nevertheless, the elderly patient does not tolerate drug toxicity as well as the younger patient. High dose therapy in patient >60 years should be administered only after careful risk benefit evaluation...

- Inflammation and ulcers of the gullet
- Severe bowel inflammation (necrotising colitis)
- Bowel cysts
- Ulceration of the skin
- Itching
- Inflammation at the site of injection
- Brown/black spots on the skin (lentigo)
- Yellowish skin and eye balls (jaundice)
- Lung infection (pneumonia)
- Breathing difficulty
- Paralysis of the legs and lower body can occur when cytarabine is given into the space surrounding the spinal cord
- Muscle and joint pain
- Inflammation of the lining that surrounds the heart (pericarditis)
- Impaired kidney function
- Inability to pass urine (urinary retention)
- Chest pain
- Burning pain of palms and soles

Very Rare (may affect up to 1 in 10,000 people):
- Inflammation of sweat glands
- Irregular heartbeat (arrhythmias)

Not Known (frequency cannot be estimated from the available data):
- Damage to nervous tissue (Neural Toxicity) and inflammation of one or more nerves (neuritis)
- Inflammation of the pancreas (Pancreatitis)
- Sore eyes (conjunctivitis)

Other side effects:
The Cytarabine Syndrome may occur 6-12 h after the start of treatment. The symptoms include:
- Fever
- Bone and muscle pain
- Occasional chest pain
- Rash
- Sore eyes (conjunctivitis)
- Nausea (feeling sick)

Your doctor may prescribe corticosteroids (anti-inflammatory medicines) to prevent or treat these symptoms. If they are effective, treatment with cytarabine may be continued.

Reactions observed with higher-dose therapy
Central nervous system:
The following symptoms, which are usually reversible, may develop in up to one third of patients after treatment with high cytarabine doses:
- Personality changes
- Changed alertness
- Difficulty in speaking
- Problems of coordination
- Tremor
- Abnormal eye movements (nystagmus)
- Headache
- Peripheral motor and sensory neuropathies (damage to nerves of the peripheral nervous system)
- Confusion
- Sleepiness
- Dizziness
- Coma
- Convulsions

These side effects may occur more often:
- in elderly patients (>55 years of age)
- in patients with impaired liver and kidney functions
- after previous cancer treatment to the brain and spinal cord for instance radiotherapy or injection of cytostatic
- with alcohol abuse

The risk of nervous system damages increases if the cytarabine treatment:
- is given at high doses or at short intervals
- is combined with other treatments that are toxic to the nervous system (such as radiotherapy or methotrexate)

Digestive tract:
Especially in treatment with high doses of cytarabine more severe reactions may appear in addition to the common symptoms. Perforation, death of tissue (necrosis) and obstruction of the bowel and inflammation of the inner belly lining have been reported. Liver abscesses, liver enlargement, blockage of liver veins and inflammation of the pancreas have been observed after high-dose therapy. The side effects on the digestive tract are less if cytarabine is given by infusion.

Lungs:
Acute, distressing breathing difficulties and water in the lungs (pulmonary edema) have been observed, particularly at high doses.

Others:
- Heart muscle disease (cardiomyopathy)
- Abnormal muscle breakdown (rhabdomyolysis)
- Blood infection (sepsis)
- Corneal toxicity
- Viral, bacterial etc infections
- Loss of sperm and menstrual cycle

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.

For UK - You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

For Malta- ADR Reporting
The Medicines Authority
Post-Licensing Directorate
203 Level 3, Rue D'Argens, GŻR-1368 Gżira
Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

For Ireland - Reports may be made by following the links to the online reporting option accessible from the IMB homepage, or by completing the downloadable report form also accessible from the IMB website, which may be completed manually and submitted to the IMB via freepost, to the following address:
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

5. How to store Cytarabine injection

Keep out of the reach and sight of children.
Do not store above 25° C.
Do not refrigerate or freeze.
Do not use Cytarabine injection after the expiry date on the vial or carton label (mm/yy). The expiry date refers to the last day of that month.
In use Stability: Chemical and physical in-use stability has been demonstrated in sodium chloride injection (0.9 % w/v) and dextrose injection (5% w/v) for up to 24 hours at temperature below 25° C and for up to 72 hours at 2-8° C..
From a microbiological point of view, the product should be used immediately. If not used, 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 condition.
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 injection contains:
Cytarabine injection contains the active ingredient Cytarabine.
1 ml contains 100 mg 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.
Each 40 ml vial contains 4 g of Cytarabine.
Each 50 ml vial contains 5 g of Cytarabine.
The other ingredients are Macrogol 400, Trometamol, and water for injections.

What Cytarabine injection looks like and contents of the pack:
Cytarabine injection is a clear, colourless solution for injection or infusion..
For 1 ml,
Solution for injection is filled in 2 ml Type - I clear glass vial closed with 13 mm grey rubber stopper and 13 mm aluminium flip-off transparent blue seal/13 mm aluminium flip off royal blue seal.
For 5 ml,
Solution for injection is filled in 5 ml Type - I clear tubular glass vial closed with 20 mm grey rubber stopper and 20 mm aluminium flip-off transparent blue seal/20 mm aluminium flip off royal blue seal.
For 10 ml,
Solution for injection is filled in 10 ml Type - I clear tubular glass vial closed with 20 mm grey rubber stopper and 20 mm aluminium flip-off transparent blue seal/20 mm aluminium flip off royal blue seal.
For 20 ml,
Solution for injection is filled in 20 ml Type-I clear glass vial closed with 20 mm grey rubber stopper and 20 mm aluminium flip off royal blue seal.
For 40 ml,
Solution for injection is filled in 50 ml Type-I clear moulded glass vial closed with 20 mm grey rubber stopper and 20 mm aluminium flip off royal blue seal.
For 50 ml,
Solution for injection is filled in 50ml Type-I clear moulded glass vial closed with 20 mm grey rubber stopper and 20 mm aluminium flip off violet seal.

Pack sizes:
1 x 1 ml vial, 5 x 1 ml vial, 1 x 5 ml vial, 5 x 5 ml vial
1 x 10 ml vial, 1 x 20 ml vial, 1 x 40 ml vial
1 x 50 ml vial
Not all pack sizes may be marketed.

Marketing Authorisation Holder and manufacturer:
Accord Healthcare Limited,
Sage House, 319 Pinner Road, North Harrow, HA1 4HF,
United Kingdom.

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

Name of the Member State	Name of the medicinal product
United Kingdom	Cytarabine 100 mg/ml Solution for Injection or Infusion
Bulgaria	Цитарабин Акорд 100 mg/ml инжекционен или инфузионен разтвор
Estonia	Cytarabine Accord 100 mg/ml süste- või infusioonilahus
Lithuania	Cytarabine Accord 100 mg/ml injekcinis/ infuzinis tirpalas
Latvia	Cytarabine Accord 100 mg/ml šķīdums injekcijām vai infūzijām
Austria	Cytarabin Accord 100 mg/ml Injektions-/ Infusionslösung
Belgium	Cytarabine Accord Healthcare 100 mg/ml Oplossing voor injectie of infusie
Cyprus	Cytarabine Accord 100 mg/ml Solution for Injection or Infusion
Czech Republic	Cytarabine Accord 100 mg/ml injekční nebo infuzní roztok
Germany	Cytarabine Accord 100 mg/ml Lösung zur Injektion oder Infusion
Denmark	Cytarabine Accord 100 mg/ml
France	Cytarabine Accord 100 mg/ml solution injectable/pour perfusion
Hungary	CYTARABINE Accord 100 mg/ml oldatos injekció vagy infúzió
Ireland	Cytarabine 100 mg/ml Solution for Injection or Infusion
Italy	Citarabina Accord
Malta	Cytarabine 100 mg/ml Solution for Injection or Infusion
The Netherlands	Cytarabine Accord 100 mg/ml, oplossing voor injectie of infusie
Norway	Cytarabine Accord
Poland	Cytarabina Accord
Portugal	Citarabina Accord
Slovak Republic	Cytarabine Accord 100 mg/ml Solution for Injection or Infusion
Sweden	Cytarabine Accord 100 mg/ml Lösningen för injektion eller infusion

This leaflet was last revised in 08/2014.

Incompatibilities
Incompatibilities with: Carbenicillin sodium, cephanothin sodium, gentamicin sulphate, Heparin sodium, hydrocortisone sodium succinate, insulin regular, Methotrexate, 5-fluorouracil, nafcillin sodium, oxacillin sodium, penicillin G sodium (benzyl penicillin), and methyl-prednisolone sodium succinate and prednisolone sodium.

Instruction for Use/Handling
For single use only.
If solution appears discoloured or contains visible particles, it should be discarded.
Once opened, the contents of each vial must be used immediately. Discard any unused contents.
Water for injections, 0.9% w/v saline or 5% w/v dextrose are commonly used infusion fluids for Cytarabine (see Section 6.3). Cytarabine injection should not to be mixed any other medicinal products except those mentioned in section 6.6.

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

Disposal and Contamination:
Any unused product or waste material should be disposed of in accordance with local requirements.
To destroy, place in a high risk (for cytotoxics) waste disposal bag and incinerate at 1100°C.
Any unused product or waste material should be disposed of in accordance with local requirements.
If spills occur, restrict access to the affected area and adequate protection including gloves and safety spectacles should be worn. Limit the spread and clean the area with absorbent paper/material. Spills may also be treated with 5% sodium hypochlorite. The spill area should be cleaned with copious amounts of water. Place the contaminated material in a leak proof disposal bag for cytotoxics and incinerate at 1100°C.

Shelf life
2 years
In use stability: Chemical and physical in-use stability has been demonstrated in sodium chloride injection (0.9 % w/v) and dextrose injection (5% w/v) for up to 24 hours at temperature below 25° C and for up to 72 hours at 2-8° C
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 24 hours at 2-8° C, unless dilution has taken place in controlled and validated aseptic conditions.

Storage
Do not store above 25° C.
Do not refrigerate or freeze.