Cytosar®
(Cytarabine)

1. NAME OF THE MEDICINAL PRODUCT

CYTOSAR

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder freeze dried and diluent for solution for injection, containing cytarabine 500 mg. Diluent is 10 ml water for injection packaged in ampoules. Diluent contains benzyl alcohol (see Section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Gasping Syndrome and Section 4.6 FERTILITY, PREGNANCY AND LACTATION). One 10 mL ampoule contains 90 mg of benzyl alcohol.

Powder freeze dried for solution for injection, containing cytarabine 100 mg.

3. PHARMACEUTICAL FORM

500mg: Powder freeze dried and diluent for solution, for injection.
100mg: Powder freeze dried for solution, for injection

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

- Acute myeloblastic leukaemias of adult and children.
- Acute lymphoblastic leukaemias and meningeal localisation of the disease.
- Acute transformation of chronic myeloid leukaemia and myelodysplasias.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Posology and method of administration differ in accordance with the drug combination protocols.

Posology

Many therapeutic protocols using cytarabine have been proposed:

Acute myeloblastic leukaemias and acute transformation of chronic myeloid leukaemias and of myelodysplasias:

Dosages available in mg/m² of body surface area are usable for adults and children.

Induction:

Combination chemotherapy (always with anthracycline, sometimes with other antineoplastic agents):

- 100 mg/m²/d during 7 to 10 days
- 200 mg/m²/d during 5 to 7 days.

A second cycle can be administrated if the first has failed.

Maintenance and consolidation

The chemotherapy protocol which has led to remission can be used for consolidation. Cytarabine can be administered at lower doses, alone or in combination with other antineoplastic agents, in cycles spaced 4 to 6 weeks apart, during maintenance treatment.

Subcutaneous route can be used for maintenance treatment: 20 mg/m²/day, administered in 1 or 2 injections during 5 to 10 days.

Acute lymphoblastic leukaemias

Induction and maintenance treatment

Protocols are similar to those used for acute myeloid leukaemia treatment. Combinations mostly include cytarabine-vincristine-prednisolone.

Meningeal location treatment using intrathecal route

As a preventive measure, cytarabine is used at 20 mg/m², and can be combined with methotrexate and hydrocortisone.

For children younger than 3 years of age, the dosage is 30 mg/m².

As a curative measure, cytarabine is usually used at 20 mg/m², once to twice a week.

Cytarabine must be administered in hospitals, under close medical supervision.

Before use, cytarabine can be reconstituted using the following solvent:

water for injection.

The following volumes of solvent should be used for reconstitution:

- cytarabine 500 mg should be reconstituted with 10 ml of solvent.
- cytarabine 1 g should be reconstituted with 10 ml of solvent.
- cytarabine 2 g should be reconstituted with 20 ml of solvent.

At this high dose, cytarabine 500 mg is administered by intravenous infusion in 250 ml of isotonic glucose solution of isotonic sodium chloride solution over 1 to 3 hours, at a dose of 2 to 3 g/m² every 12 hours; equivalent to 4 to 6 g/m²/24 hours during 6 days (for a total of 12 doses per cycle).

Do not use solvents containing benzyl alcohol. Benzyl alcohol should not be used for solution reconstitution in the case of intrathecal administration or for administration in newborns and children less than 3 years old (see section 4.2 in Method of administration).

DOSAGE ADJUSTMENT

- The frequency of cycles depends on the response to therapy and on hematologic and extra-hematologic toxicity.
- Repeated blood and bone marrow examination should be performed, especially at the beginning of the treatment. Hepatic and renal function should also be monitored.
- Dosage adjustment is based on the results of blood and bone marrow examination (myelogram). Usually, therapy is discontinued if:
  - the platelet count is below 50,000/mm³,

- the neutrophil count is below 1,000/mm³.

- Therapy may be restarted once the blood count permits it and when blast cells reappear in the blood or bone marrow. Patients whose treatment is withheld until normal blood values are attained may later escape from disease control.
- The dosage should also be modified if toxicity other than hematologic toxicity occurs and in cases of combination with other chemotherapeutic agents. Cytarabine can be used alone and in combination. Several therapeutics protocols can be used. ARA-C, at a dose of 3 g/m² by IV infusion over 1 to 3 hours every 12 hours during 4 to 6 days has been associated with adriamycin (30mg/m² D6 and D7), asparaginase (6,000 units/m²), rubidazone, AMSA (150 to 200 mg/m²/day x 3), with significant therapeutics results.

  Hematologic toxicity is often more pronounced, as well as gastrointestinal toxicity, particularly mucositis.

  Warning

  It is extremely important to take care that administration is intravenous. Any extravasation may give rise to necrosis of surrounding tissues. Should extravasation occur, the infusion should be stopped immediately.

  Manipulation modalities

  The preparation of cytotoxic parenteral solutions must obligatorily be conducted by specialized and trained personnel with knowledge of the drugs used under conditions ensuring environmental protection and, especially, protection of the personnel handling the drugs. Preparation requires a dedicated facility. Smoking, eating and drinking in that facility are prohibited. Operatives must be equipped with a set of appropriate equipment for the procedures, particularly long-sleeved laboratory coats, protective masks, mobcaps, protective glasses, single-use-disposable sterile gloves, protective fields for the work surface, waste bags and containers. Excreta and vomit are to be handled with caution. Pregnant women must be warned and avoid handling cytotoxic products. All broken containers must be processed with the same precautions and considered contaminated waste. Disposal of contaminated wastes is conducted by incineration in appropriately-labelled rigid containers.

  These provisions may be made in the context of the oncological network (DGS/DH/98 circular No. 98/188 dated March 24, 1998) in cooperation with an appropriate structure fulfilling the required conditions.

Method of administration

Cytarabine can be administrated using several administration routes.

- intravenous route by direct injection or continuous perfusion: higher total doses of cytarabine can be better tolerated when administered by rapid IV injection as compared to slow infusion. Such a phenomenon can be explained by the rapid inactivation of the drug and the brief exposure of susceptible normal and neoplastic cells to significant levels after rapid injection;
- subcutaneous route: cytarabine is particularly well tolerated. Pain and inflammation at injection sites are very rarely observed;
- intrathecal route: cytarabine is used in the preventive and curative treatment of acute lymphoblastic leukaemia of meningeal localisation in children.

Benzyl alcohol should not be used for solution reconstitution in the case of intrathecal administration or in the case of intravenous administration at high doses or for administration in neonates or children under 3 years (see sections 4.3. CONTRAINDICATIONS and 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE). The reconstitution is done with CSF autologous or with an isotonic sodium chloride solution, the use needs to be immediate.

Clinical experience suggests that the results obtained with cytarabine, whatever the route of administration, are closely related to the dose modifications in order to destroy the most blast cells with minimal toxicity. Multidrug chemotherapy involves dose modifications for each of the constituents of the protocol.

Handling procedures

The preparation of cytotoxic parenteral solutions must obligatorily be conducted by specialized and trained staff with knowledge of the drugs used, under conditions ensuring environmental protection and, especially, protection of the personnel handling the drugs. Preparation requires a dedicated facility. Smoking, eating and drinking in that facility are prohibited. Operatives must be equipped with a set of appropriate equipment for the procedures, particularly long-sleeved laboratory coats, protective masks, mobcaps, protective glasses, single-use-disposable sterile gloves, protective fields for the work surface, waste bags and containers. Excreta and vomit are to be handled with caution. Pregnant women must be warned and avoid handling cytotoxic products. All broken containers must be processed with the same precautions and considered contaminated waste. Disposal of contaminated wastes is conducted by incineration in appropriately-labelled rigid containers.

These provisions may be made in the context of the oncological network (DGS/DH/98 circular No. 98/188 dated March 24, 1998) in cooperation with an appropriate structure fulfilling the required conditions.

Instructions for opening ampoules correctly

Important: the ampoule is pre-scored at the neck. The coloured dot on the bulb enables you to position it correctly (Figure 1). Hold the ampoule with the coloured dot towards you. The ampoule snaps open easily if you place your thumb on the coloured dot and bend it slightly downwards (Figure 2). Do not break the ampoule open at the line.

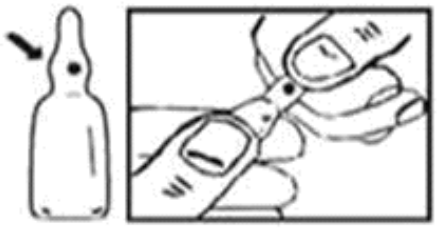


Figure 1

Figure 2

4.3. CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Those common to all cytotoxic therapies.

- Pre-existing bone marrow suppression.
- Toxic degenerative encephalopathies, particularly after treatment with methotrexate or ionizing radiation.
- Patients with a progressive meningeal infection.
- Breastfeeding (see section 4.6. FERTILITY, PREGNANCY AND LACTATION).
- Attenuated live vaccines (against yellow fever, chickenpox – zona, measles, mumps, rubella, tuberculosis, rotavirus, flu) and this until 6 months following the discontinuation of the chemotherapy (see section 4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION): risk of widespread, potentially fatal vaccine disease.
- Solvents containing Benzyl alcohol must not be used to reconstitute the solution for intrathecal administration or high dose intravenous administration. For other types of administration, the solution reconstituted with the solvent is contraindicated in neonates and children under 3 years.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cytarabine must be administered under close medical supervision, particularly during induction treatment: blood and bone marrow examination (myelogram) must be performed and repeated in order to evaluate therapeutic results and hematologic toxicity of the treatment.

Cytarabine is a powerful myelosuppressive agent: it can cause medullary hypoplasia or aplasia, the severity of which depends on the dose administered and the treatment schedule utilised.

Pre-existing bone marrow suppression: cytarabine can be administered in case of absolute necessity.
In this case the treatment must be commenced with caution.
Patients receiving this treatment must be kept under close medical supervision.

During the induction phase, white blood cell and platelet counts must be performed on a daily basis. Frequent medullary examinations must be conducted once the blast cells have disappeared from the peripheral blood.

Suspending or modifying the treatment must be considered if drug-induced bone-marrow impairment leads to a reduction in the number of platelets to less than 50,000 or in the number of polynuclear neutrophils to less than 1000/mm^3. The cell count may continue to decrease after treatment is stopped, reaching minimum levels after a treatment-free period of 12-24 days. If this is indicated, treatment can recommence when clear signs of medullary repair appear.

Special equipment must be available to manage the potentially fatal complications stemming from bone-marrow impairment (infections resulting from granulocytopenia and other reduction in the body's natural defences, haemorrhages secondary to thrombocytopenia).

Hepatic and renal function should be monitored. Patients with hepatic or renal insufficiency have an increased risk of toxicity to the central nervous system after the administration of heavy doses of cytarabine. When administering the product to patients with from hepatic and renal insufficiency, caution must be used by reducing the dose.

Tumour lysis syndrome: like every antileukemia chemotherapy, cytarabine induce hyperuricemia secondary to cell lysis: uric acid concentration in blood should be monitored during treatment and hyperuricemia must be prevented.

Neurological: cases of severe neurological adverse reactions that ranged from headache to paralysis, coma and stroke-like episodes have been reported mostly in juveniles and adolescents given intravenous cytarabine in combination with intrathecal methotrexate.

Patients receiving high doses of cytarabine must be monitored for signs of neuropathy, for it may be necessary to modify the administration and dosing regimen to avoid irreversible neurological disorders (see section 4.8. UNDESIRABLE EFFECTS).

Vaccination with a live vaccine is contraindicated in patients receiving cytarabine (see section 4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION).

Combining this medicine with phenytoin (and, by extrapolation, fosphenytoin) is not recommended (see section 4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION).

Treating women of childbearing potential (see section 4.6. FERTILITY, PREGNANCY AND LACTATION):

Women of childbearing potential treated with cytarabine must use effective contraception during the treatment and for a month after its completion.

Treating men (see section 4.6. FERTILITY, PREGNANCY AND LACTATION):

Men treated with cytarabine or their partners should ideally use a contraceptive method to avoid conception during the treatment and for three months after its completion.

Patients must be advised to seek advice about storing sperm before undergoing treatment because of the possibility that it will impair their fertility.

Toxicity related to benzyl alcohol

A solvent ampoule of 5 ml contains 47.25 mg of benzyl alcohol. This solvent must not be utilised to reconstitute the solution for intrathecal administration or high dose intravenous administration and in neonates and children under 3 years.

The solution reconstituted with this solvent can cause toxic and anaphylactoid reactions in infants and children under 3 years.

The reconstitution is done with CSF autologous or with an isotonic sodium chloride solution; the use needs to be immediate.

Intrathecal route

When administered intrathecally, cytarabine can be associated with nausea, vomiting, and serious toxicity to the central nervous system that can result in permanent damage, including blindness and other neurological toxicities.

It is not recommended to exceed the individual validated dose, and great care must be taken with patients who have previously undergone radiotherapy or intrathecal treatment (see section 4.8. UNDESIRABLE EFFECTS).

Excipients

Benzyl alcohol

Solvent of this medicine product contains benzyl alcohol. The preservative benzyl alcohol may cause hypersensitivity reactions. Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in paediatric patients including neonates ("gasping syndrome"). Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", The minimum amount of benzyl alcohol at which toxicity may occur is not known. Benzyl alcohol containing formulations should only be used in neonates if it is necessary and if there are no alternatives possible. Premature and low-birth weight neonates may be more likely to develop toxicity. Benzyl alcohol containing formulations should not be used for more than 1 week in children under 3 years of age unless necessary. If use of a benzyl alcohol-containing formulation of ARACYTINE is necessary, it is important to consider the combined daily metabolic load of benzyl alcohol from all sources, especially in patients with liver or kidney impairment, as well as in pregnant or breast-feeding women, because of the risk of accumulation and toxicity (metabolic acidosis).

Benzyl alcohol-free formulations of ARACYTINE are available.

Sodium

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

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Interactions with medicinal product

Due to the increased risk of thrombosis associated with tumorous disease, the use of anticoagulant treatment is common. The wide intra-individual variability in blood clotting parameters during these diseases, in addition to a possible drug interaction between oral anticoagulants and cancer chemotherapeutic agents, requires more frequent determination of the INR if the patient is to be treated with oral anticoagulants (acenocoumarol, fluindione, phenindione, tioclomarol, warfarin).

Interactions which are common to every cytotoxics

Contraindicated associations (see section 4.3. CONTRAINDICATIONS)

+ Live attenuated vaccines (against yellow fever, chickenpox – zona, measles, mumps, rubella, tuberculosis, rotavirus, flu) and this until 6 months following the discontinuation of the chemotherapy: vaccination against yellow fever

Risk of potentially fatal generalized vaccine disease.

Inadvisable associations (see section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

+ Phenytoin (and by extrapolation fosphenytoin)

Risk of seizures due to decreased gastrointestinal absorption of phenytoin caused by the cytotoxic drug, or else risk of increased toxicity or loss of efficacy of the cytotoxic drug due to an increase in its hepatic metabolism induced by phenytoin or fosphenytoin.

Associations requiring precautions for use

+ Vitamin K antagonists

Increased risk of thrombotic and haemorrhagic disorders in the tumor. In addition, possible interaction between antivitamin K and chemotherapy.

More frequent monitoring of INR.

Associations to be taken into account

+ Immunosuppressants (ciclosporin, everolimus, sirolimus, tacrolimus, temsirolimus)

Profound immunodepression with risk of lymphoproliferative syndrome.

4.6. FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Women of childbearing potential treated with cytarabine must use effective contraception during the treatment and for a month after its completion.

Given the available data, cytarabine will not be administered during pregnancy unless the pathology is life-threatening for the mother. Studies of the reproduction functions conducted on various animal species have shown that cytarabine is embryotoxic and has teratogenic effects, principally on the brain and skeleton.

Some cases of congenital malformations of the limbs and the outer ear have been reported after exposure in the first trimester of pregnancy. In the event of exposure in the first trimester, focused ultrasound checks are accordingly recommended.

Cases of prematurity or delayed intra-uterine growth have been reported.

Cases of jaundice, bone-marrow impairment and transitory hypereosinophilia have been reported at birth. Biological monitoring is therefore indicated in the first weeks of life.

Solvent of ARACYTINE contains benzyl alcohol as a preservative. Benzyl alcohol can cross the placenta (see section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Breast-feeding

There are no known cases of the excretion of cytarabine in breast milk. Because of the potentially serious side effects that cytarabine may have on breast-fed infants, taking cytarabine must be contraindicated during breast-feeding.

Solvent of ARACYTINE contains benzyl alcohol as a preservative. Benzyl alcohol present in maternal serum is likely to cross into human milk and may be orally absorbed by a nursing infant (see section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Fertility

Cytarabine is mutagenic, and it may cause chromosome damage to spermatozoa.

Patients must be advised to seek advice about storing sperm before undergoing treatment because of the possibility that it will impair their fertility.

Men treated with cytarabine or their partners should ideally use a contraceptive method to avoid conception during the treatment and for three months after its completion.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Effects on the ability to drive and use machines have not been studied. On the basis of the undesirable effects reported, however, patients must be warned not to drive or operate machinery without first consulting a healthcare professional.

4.8. UNDESIRABLE EFFECTS

Summary of the safety profile

Blood and lymphatic system disorders

Cytarabine is an antineoplastic agent that induces myelosuppression. Its administration thus brings about bone-marrow suppression or depression, leading to anaemia, granulocytopenia**,** thrombopenia, megaloblastosis and a fall in the reticulocyte rate.

The severity of the bone-marrow suppression depends on the dose administered and on the treatment schedule utilised. In relation to aplasia, chemotherapy treatment may be followed by serious secondary haemorrhagic or infectious complications.

Infections and infestations

Viral, bacterial, fungal, parasitic and saprophytic infections may be associated with the use of cytarabine, either on its own or in combination with other immunosuppressant medicine affecting cellular or humoral immunity. These infections may be mild, but they can also be serious and sometimes fatal.

Respiratory, thoracic and mediastinal disorders:

Rare cases of pneumatosis intestinalis have been reported in patients treated with intermediate doses of cytarabine, either on its own or in combination with other chemotherapy drugs, though no link with cytarabine has been clearly established.

Gastrointestinal disorders

Nausea and vomiting are frequently associated with the use of cytarabine,
Some cases of acute pancreatitis have been reported in patients treated with cytarabine in combination with other medicine.

Musculoskeletal and connective tissue disorders

A cytarabine syndrome has been described by a thermic elevation, myalgia, bone pain associated in certain cases to thoracic pain, maculopapular rashes, conjunctivitis and general unwell state. This syndrome appears 6 to 12 hours after the administration of the medicinal product.
Its treatment and prevention respond to corticosteroids.

Investigations

In rare cases, blastolysis secondary hyperuricemia can be induced by treatment with cytarabine, requiring monitoring uric acid levels in the blood and urine.

Safety data are derived from internal pharmacovigilance database and literature research.

Adverse reactions table (conventional and high doses)

The reported adverse reactions are listed below by MedDRA System Organ Class and by frequency.

Frequencies are defined as: very common (≥ 1/10), Common (≥ 1/100 à < 1/10), uncommon (≥ 1/1 000 à < 1/100), rare (≥ 1/10 000 à < 1/1 000), and frequency not known (cannot be estimated from available data).

Infections and infestations	
Very common	Sepsis, pneumonia, infection [a]
Frequency not known	Injection site cellulite
Blood and lymphatic system disorders	
Very common	Aplasia, Bonne marrow failure, thrombocytopenia, anaemia, anaemia megaloblastic, leukopenia, reticulocyte count decreased
Immune system disorders	
Frequency not known	Anaphylactic reaction, allergic oedema
Metabolism and nutrition disorders	
Common	Decreased appetite
Nervous system disorders	
Frequency not known	Neurotoxicity, neuritis, dizziness, headache
Eye disorders	
Frequency not known	Conjunctivitis (see cytarabine syndrome) [b]
Cardiac disorders	
Frequency not known	Pericarditis, sinus bradycardia
Vascular disorders	
Frequency not known	Thrombophlebitis
Respiratory, thoracic and mediastinal disorders	
rare	Interstitial pneumopathy
Frequency not known	Dyspnoea, oropharyngeal pain
Gastrointestinal disorders	
Very common	Stomatitis, mouth ulceration, anal ulcer, anal inflammation, diarrhoea, vomiting, nausea, abdominal pain, mucitis
Frequency not known	Pancreatitis, oesophageal ulcer, oesophagitis
Hepatobiliary disorders	
Very common	Hepatic function abnormal
Frequency not known	Jaundice
Skin and subcutaneous tissue disorders	
Very common	Alopecia, rash
Common	Skin ulcer

Frequency not known	Palmar-plantar erythrodysaesthesia syndrome, urticaria, pruritus, ephelides, exfoliative dermatitis
Musculoskeletal, connective tissue and bone disorders	
Very common	Cytarabine syndrome
Renal and urinary disorders	
Frequency not known	Renal impairment, Urinary retention
Reproductive system and breast disorders	
Frequency not known	Amenorrhea, azoospermia.
General disorders and administration site conditions	
Very common	Pyrexia
Frequency not known	Injection site reaction [c]
Investigations	
Very common	Biopsy bone marrow abnormal, blood smear test abnormal
Rare	Hyperuricaemia

[a] may be mild, but can be severe and at times fatal
[b] may occur with rash and may be haemorrhagic with high dose therapy
[c] pain and inflammation at subcutaneous injection site

Description of specific adverse reactions

Secondary effects and toxicity of the intrathecal delivery route

The most frequently reported effects following intrathecal administration are nausea, vomiting and fever. These reactions are mild.

Severe cases of neurotoxic events, including paraplegia, have been reported when intrathecal administration has been combined with methotrexate and corticosteroids, and when intrathecal injection has been combined with the systemic administration of heavy doses of methotrexate and cytarabine.

Some cases of necrotising leukoencephalitis have been reported, with and without convulsions. Some of these patients have also been treated with methotrexate and/or hydrocortisone by the intrathecal route and by brain irradiation.

Two cases of blindness have been described in subjects in remission after intravenous multidrug chemotherapy and preventive treatment of the meningeal grafts with intrathecal cytarabine and brain radiotherapy.

Adverse reactions table (high doses)

Nervous system disorders

Neurological toxicity in large doses.

Cerebellar deficiencies in the form of dysarthria or nystagmus at a minimum, or of major ataxia at a maximum, the onset of which may be delayed, and may be permanent. Incidences of coma, behavioural disorders and peripheral sensory and motor neuropathies have also been reported. Serious and indeed

fatal cases have been observed in patients who have previously undergone other treatments of the central nervous system (brain irradiation): it is not recommended to exceed the individual validated dose, and great care must be taken with patients who have previously undergone radiotherapy or intrathecal treatment.

There seems to be a correlation between neurological toxicity and a high administration rate.

Eye disorders

Reversible disorders of the cornea and haemorrhagic conjunctivitis have been described after the administration of large doses of cytarabine. These phenomena can be prevented or alleviated by the instillation of eye drops containing corticoids.

Cardiac disorders

Cases of cardiomyopathy with the potential to be fatal have been reported following the experimental use of a treatment combining large doses of cytarabine and cyclophosphamide, which is used in connection with bone-marrow transplants.

Respiratory, thoracic and mediastinal disorders

Severe pulmonary toxicity, potentially fatal, syndrome of pulmonary distress, pulmonary oedema have been observed after the use of high doses of cytarabine.

Table of adverse reactions (high doses only)

The reported adverse reactions are listed below by MedDRA System Organ Class and by frequency.

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 à < 1/10), uncommon (≥ 1/1 000 à < 1/100), rare (≥ 1/10 000 à < 1/1 000), and frequency not known (cannot be estimated from available data).

Infections and infestations	
Frequency not known	Liver abscess
Nervous system disorders	
Very common	Cerebral disorder, cerebellar disorder, somnolence
Frequency not known	Coma, convulsion, peripheral motor neuropathy, peripheral sensory neuropathy
Eye disorders	
Very common	Corneal disorder
Cardiac disorders	
Frequency not known	Cardiomyopathy [a]
Respiratory, thoracic and mediastinal disorders	
Very common	Acute respiratory distress syndrome, pulmonary oedema, pulmonary toxicity
Gastrointestinal disorders	
Common	Necrotising colitis

Frequency not known	Gastrointestinal necrosis, gastrointestinal ulcer, pneumatosis intestinalis, peritonitis
Hepatobiliary disorders	
Frequency not known	Liver injury, hyperbilirubinemia
Skin and subcutaneous tissue disorders	
Common	Skin exfoliation

[a] With subsequent death

Paediatric population

The adverse reaction profile of cytarabine was similar in the paediatric population in comparison to the adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. OVERDOSE

There is no specific antidote. Doses of 4.5 g/m² by intravenous infusion over 1 hour every 12 hours for 12 doses have caused irreversible central nervous system toxicity and death.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic class: Antineoplastic agents – Antimetabolite - Pyrimidine analogue, ATC Code: L01BC01.

Antimetabolite with specificity for the S phase of the cell cycle (cell division phase).

The cytotoxicity of cytarabine results from incorporation of its active metabolite ARA-CTP into DNA which blocks DNA synthesis. DNA molecules containing ARA-CTP show structural changes that result in perturbations of cellular metabolism and alter replication. Cytotoxicity also occurs through inhibition of DNA polymerase and by an action on kinases.

The use of high doses of cytarabine has been shown to overcome the resistance of leukemic cells no longer responsive to conventional doses of the drug.

Several mechanisms appear to play a role in overcoming this resistance:

- increase in the quantity of substrate,
- increase in the intracellular pool of ARA-CTP: a positive correlation exists between intracellular uptake of ARA-CTP and the percentage of cells in the S-phase.

5.2. PHARMACOKINETIC PROPERTIES

Pharmacokinetics of cytarabine used in high doses: the pharmacokinetics of cytarabine in high doses (H.D ARA C) is bicompartmental (2-compartment model).

After the intravenous administration of a dose of 2-3 g/m² every 12 hours administered over one hour for 5-6 days (10-12 doses), plasma concentrations at the end of the infusion are about: 19.96 ± 8.02 µg/ml and 35 ± 2.8 µg/ml. Plasma concentrations decrease when infusion ceases, in line with a bi-exponential curve. Six hours after infusion ceases, the concentrations obtained correspond to those measured at the "steady-state" after a continuous infusion of 100 mg / m² of cytarabine for 24 hours.

In comparison with the kinetics of cytarabine in conventional doses, high doses produce a peak that is 200 times higher.

Similarly, the peak concentration of Ara-U inactive metabolite is retarded with high doses because it only appears after 15 minutes.

In conventional doses:

- $T_{½\,A}$ is about a few minutes (10 on average),
- $T_{½\,B}$ is about several hours (1 to 3).

Protein binding: around 14% of the cytarabine is bound to plasma proteins.

Renal clearance is slower than with high doses, about 232 ± 33.4 ml/min/m².

Cytarabine administered systemically (I.V.) crosses the blood/brain barrier: after a dose of 1-3 g/m² by infusion over 1-3 hours, concentrations in the cerebrospinal fluid are about 100-300 ng/ml.

The product also diffuses in the saliva, the spleen, the kidneys, the gastrointestinal tract, the thymus, the bone marrow and tears. It is not known whether cytarabine passes into breast milk.

Activation of cytarabine into its Ara-CTP active metabolite

Passage across the cell membrane by high-concentration diffusion, facilitated according to the concentration gradient by a mechanism utilising a weak-concentration transporter.

Enzyme activation by successive phosphorylations: the enzymes that activate the Ara-C are those that ensure activation of natural ribonucleoside, deoxycytidine.

Two enzymes play an important part: deoxycytidine kinase (Ara-C → Ara-CMP) and deoxycytidilate kinase (Ara-CMP → Ara-CDP).

The active metabolite formed is Ara-CTP (arabinofuranosylcytosine triphosphate). The formation of Ara-CTP is a necessary condition for the cytotoxicity of the product, but apparently not the only one; other mechanisms also take place.

Catabolism

Cytarabine is broken down into Ara-U (arabinofuranosyl uracil), an inactive metabolite, by cytidine deaminase, an enzyme presents in many tissues, but principally in the liver, leukemia cells and marrow. This enzyme is targeted by numerous activation and inhibition phenomena.

5.3. PRECLINICAL SAFETY DATA

Toxicity studies which have been conducted on rats and dogs by the oral, intravenous, intraperitoneal, subcutaneous and intra-articular routes have shown that targeted organs are: haematopoietic system (megaloblastosis, reticulocytopenia, leukopenia, thrombocytopenia and anaemia), brain (destruction of cerebral and cerebellar functions) and to a lesser extent liver (from moderate increase of hepatic enzymes to hepatic insufficiency) and kidneys (nephrotoxicity). The severity of toxicity is dose-dependent. The other effects which have been reported are: lung and gastrointestinal (diarrhoea, ulcerations) toxicity, cardiomyopathy, conjunctivitis and cutaneous rash.

There is no study concerning fertility, but effects of male fertility have been reported in mice. Cytarabine is embryotoxic and teratogenic (brain and skeleton) and has caused perinatal and postnatal toxicity in many species. Administered to newborn rats at a dose of 4 mg/kg/d, cytarabine has provoked developmental delays.

Cytarabine is mutagenic and clastogenic.

No studies on carcinogenesis have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Solvent: benzyl alcohol, water for injection.

6.2. INCOMPATIBILITIES

Cytarabine shows physico-chemical incompatibility with heparin, insulin, methotrexate, 5-fluorouracil, nafcillin, oxacillin, penicillin G, solu-B (B group, C and PP vitamin solution for injection), and methylprednisolone hemisuccinate.

This medicinal product should not be mixed with other medicines, except those mentioned in the section 4.2. Make sure of the compatibility before mixing or associating ARACYTINE to any other substance.

6.3. SHELF LIFE

Please see pack for expiry of product.

The reconstituted solution of cytarabine contains no antimicrobial agents. Therefore, it is recommended that the reconstitution is effectuated immediately prior to use and that the infusion is started as soon as practicable after preparation of the admixture.
Infusion should be completed within 24 hours of preparation and the residue discarded.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store at a temperature below 25 °C.
For storage conditions after reconstitution of the medicinal product, see section 6.3. SHELF LIFE.

6.5. NATURE AND CONTENTS OF CONTAINER

100 mg in vial (glass): box of 1 or 10 vials.

500 mg in vial (glass) co-packed with diluent; box of 1 or 10 vials.

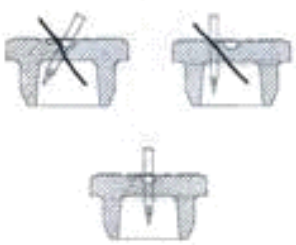
Not all pack sizes may be marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Do not use a solution which appears cloudy.

The reconstitution needs to be done using a syringe with a needle having an external diameter of 0.8 mm (equivalent to 21 gauge). The use of a higher diameter needle may lead to the cap or fragment of the cap to be dropped into the vial.

Using this needle, pierce the centre of the seal in a perpendicular manner to the cap as described in the figure below:



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

6.7. DRUG PRODUCT SPECIFICATION

Please see pack for specification.

Cytosar/LPD/PK-01
According to France approved label dated: 27July 2022 & approved information in Pakistan

7. MARKETING AUTHORIZATION HOLDER

Pfizer Pakistan Limited.
*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*