CYTOSAR CS™

1. NAME OF THE MEDICINAL PRODUCT

CYTOSAR CS™

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pack size 20 mg/mL: Solution for Injection, containing cytarabine 20 mg per mL.

Pack size 100 mg/mL: Solution for Injection, containing cytarabine 100 mg per mL.

3. PHARMACEUTICAL FORM

Sterile solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cytarabine is indicated primarily for induction and maintenance of remission in acute non-lymphocytic leukemia of both adults and children. It has also been found useful in the treatment of other leukemias, such as acute lymphocytic leukemia, and chronic myelocytic leukemia (blast phase). Cytarabine may be used alone or in combination with other antineoplastic agents, the best results are often obtained with combination therapy. Remissions induced by cytarabine not followed by maintenance treatment have been brief.

Cytarabine has been used experimentally in a variety of neoplastic diseases. In general, few patients with solid tumors have benefited.

Children with non-Hodgkin's lymphoma have benefited from a combination drug program (LSA2L2) that includes cytarabine.

Cytarabine in a high dose regimen, with or without additional cancer chemotherapeutic agents, has been shown to be effective in the treatment of poor-risk leukemia, refractory leukemia, and relapsed acute leukemia.

Cytarabine alone or in combination with other drugs (methotrexate, hydrocortisone sodium succinate) is used intrathecally for prophylaxis or treatment of meningeal leukemia.

4.2 Posology and Method of Administration

Cytarabine is not active orally. The schedule and method of administration varies with the program of therapy to be used. Cytarabine may be given by intravenous infusion or injection, subcutaneously (SC), or intrathecally.

Thrombophlebitis has occurred at the site of drug injection or infusion in some patients and rarely patients have noted pain and inflammation at subcutaneous injection sites. In most instances, however, the drug has been well tolerated.

Patients can tolerate higher total doses when they receive the drug by rapid intravenous injection as compared with slow infusion. This phenomenon is related to the drug's rapid inactivation and brief exposure of susceptible normal and neoplastic cells to significant levels after rapid injection. Normal and neoplastic cells seem to respond in somewhat parallel fashion to these different modes of administration and no clear-cut clinical advantage has been demonstrated for either.

Conventional dose: In the induction therapy of acute non-lymphocytic leukemia, the usual cytarabine dose in combination with other anti-cancer drugs is 100 mg/m^2/day by continuous IV infusion (Days 1-7) or 100 mg/m^2 IV every 12 hours (Days 1-7).

High dose: 2-3 g/m^2 as an IV infusion over 1-3 hours given every 12 hours for 2-6 days with or without additional cancer chemotherapeutic agents. If high dose therapy is used, do not use diluents containing benzyl alcohol (see Sections 4.4 Special Warnings and Precautions for Use and 6.3 Shelf Life).

SC dose: Generally 20-100 mg/m^2 depending on the indication being treated and the regimen being used.

The literature should be consulted for the current recommendations for use in leukemia and pediatric non-Hodgkin's lymphoma.

Intrathecal use in meningeal leukemia

When preparing cytarabine for intrathecal use, do not use diluents containing benzyl alcohol (see Section 4.4 Special Warnings and Precautions for Use). Many clinicians reconstitute with preservative-free 0.9% sodium chloride for injection and use immediately.

Cytarabine has been used intrathecally in acute leukemia in doses ranging from 5 mg/m^2 to 75 mg/m^2 of body surface area. The frequency of administration varied from once a day for 4 days to once every 4 days. The most frequently used dose was 30 mg/m^2 every 4 days until cerebrospinal fluid findings were normal, followed by one additional treatment. The dosage schedule is usually governed by the type and severity of central nervous system manifestations and the response to previous therapy.

Cytarabine has been used intrathecally with hydrocortisone sodium succinate and methotrexate, both as prophylaxis in newly diagnosed children with acute lymphocytic leukemia, as well as in the treatment of meningeal leukemia. One study has reported that prophylactic triple therapy has prevented late CNS disease and given overall cure and survival rates similar to those seen in patients in whom CNS radiation and intrathecal methotrexate was used as initial CNS prophylaxis. In this study the dose of cytarabine was 30 mg/m^2, hydrocortisone sodium succinate 15 mg/m^2, and methotrexate 15 mg/m^2 (an absolute maximum single dose of 15 mg of methotrexate). The physician should be aware of this regimen and note that methotrexate dosage in pediatric patients is otherwise based on age rather than body surface area.

Prophylactic triple therapy following the successful treatment of the acute meningeal episode may be useful. The physician should familiarize himself with the current literature before instituting such a program.

Cytarabine given intrathecally may cause systemic toxicity and careful monitoring of the hemopoietic system is indicated. Modification of the anti-leukemia therapy may be necessary. Major toxicity is rare (see Sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects). When cytarabine is administered both intrathecally and intravenously within a few days, there is an increased risk of spinal cord toxicity, however, in serious life-threatening disease, concurrent use of intravenous and intrathecal cytarabine is left to the discretion of the treating physician.

Focal leukemic involvement of the central nervous system may not respond to intrathecal cytarabine and may better be treated with radiotherapy.

Drug compatibilities

Cytarabine is compatible with following drugs, at the specified concentrations, in Dextrose 5% in water for eight hours: cytarabine 0.8 mg/mL and Sodium Cephalothin 1.0 mg/mL; cytarabine 0.4 mg/mL and prednisolone sodium phosphate 0.2 mg/mL; cytarabine 16 mcg/mL and vincristine sulfate 4 mcg/mL. Cytarabine is also physically compatible with methotrexate.

Use in children

Similar to use in adults.

4.3 Contraindications

Cytarabine is contraindicated in those patients who are hypersensitive to the drug.

4.4 Special Warnings and Precautions for Use

General

Only physicians experienced in cancer chemotherapy should use cytarabine.

For induction therapy, patients should be treated in a facility with laboratory and supportive resources sufficient to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity. The main toxic effect of cytarabine is bone marrow suppression with leukopenia, thrombocytopenia and anemia. Less serious toxicity includes nausea, vomiting, diarrhea and abdominal pain, oral ulceration, and hepatic dysfunction.

The physician must judge possible benefit to the patient against known toxic effects of this drug in considering the advisability of therapy with cytarabine. Before making this judgment or beginning treatment, the physician should be familiar with the following text.

Hematologic effects

Cytarabine is a potent bone marrow suppressant; the severity depends on the dose of the drug and schedule of administration. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression. Patients receiving this drug must be under close medical supervision and, during induction therapy, should, have leukocyte and platelet counts performed daily. Bone marrow examinations should be performed frequently after blasts have disappeared from the peripheral blood. Consider suspending or modifying therapy when drug-induced marrow depression has resulted in a platelet count under 50,000 or a polymorphonuclear granulocyte

count under 1000/mm^3. Counts of formed elements in the peripheral blood may continue to fall after the drug is stopped and reach lowest values after drug-free intervals of 12 to 24 days. When indicated, restart therapy when definite signs of marrow recovery appear. Facilities should be available for management of complications, possibly fatal, of bone marrow suppression (infection resulting from granulocytopenia and other impaired body defenses, and hemorrhage secondary to thrombocytopenia).

Anaphylactic reactions have occurred with cytarabine treatment. Anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of cytarabine.

High dose schedules

Severe, and at times fatal, CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following high dose (2-3 g/m^2) schedules of cytarabine. These reactions include reversible corneal toxicity, and hemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with a local corticosteroid eye drop; cerebral and cerebellar dysfunction usually reversible including personality changes, somnolence, convulsion and coma, severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis leading to peritonitis, sepsis and liver abscess; pulmonary edema, liver damage with increased hyperbilirubinemia; bowel necrosis; and necrotizing colitis.

Severe and sometimes fatal pulmonary toxicity, adult respiratory distress syndrome and pulmonary edema have occurred following high dose schedules with cytarabine therapy. A syndrome of sudden respiratory distress, rapidly progressing to pulmonary edema and radiographically pronounced cardiomegaly has been reported following experimental high dose therapy with cytarabine used for the treatment of relapsed leukemia.

Cases of cardiomyopathy with subsequent death have been reported following experimental high dose cytarabine and cyclophosphamide therapy when used for bone marrow transplant preparation. This may be schedule dependent.

Peripheral motor and sensory neuropathies after consolidation with high doses of cytarabine, daunorubicin, and asparaginase have occurred in adult patients with acute non-lymphocytic leukemia. Patients treated with high doses of cytarabine should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurological disorders.

Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more commonly seen with high dose therapy than with standard treatment programs of cytarabine.

When large intravenous doses are given quickly, patients are frequently nauseated and may vomit for several hours post-injection. This problem tends to be less severe when the drug is infused.

Conventional dose schedules

Abdominal tenderness (peritonitis) and guaiac positive colitis, with concurrent neutropenia and thrombocytopenia, have been reported in patients treated with conventional doses of cytarabine in combination with other drugs. Patients have responded to non-operative medical management. Delayed progressive ascending paralysis resulting in death has been reported in children with AML following intrathecal and intravenous cytarabine at conventional doses in combination with other drugs.

Hepatic and/or renal function

The human liver apparently detoxifies a substantial fraction of an administered dose of cytarabine. In particular, patients with renal or hepatic function impairment may have a higher likelihood of CNS toxicity after high-dose treatment with cytarabine. Use the drug with caution and possibly at reduced doses in patients whose liver or kidney function is poor.

Periodic checks of bone marrow, liver and kidney functions should be performed in patients receiving cytarabine.

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.

Tumor lysis syndrome

Like other cytotoxic drugs, cytarabine may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient’s blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem.

Pancreatitis

Acute pancreatitis has been reported to occur in patients being treated with cytarabine in combination with other drugs.

Immunosuppressant effects/increased susceptibility to infections

Administration of live or live-attenuated vaccines, in patients immunocompromised by chemotherapeutic agents including cytarabine, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving cytarabine. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Gasping syndrome

The preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome", and death in pediatric patients. 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. The risk of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys' capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity (see Section 4.6 Fertility, Pregnancy and Lactation). If cytarabine is used in high dose or intrathecal therapy, do not use a diluent containing benzyl alcohol. The preservative-free 0.9% sodium chloride can be used for reconstitution (see Section 4.2 Posology and Method of Administration).

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Digoxin

Reversible decreases in steady-state plasma digoxin concentrations and renal glycoside excretion were observed in patients receiving beta-acetyldigoxin and chemotherapy regimens containing cyclophosphamide, vincristine and prednisone with or without cytarabine or procarbazine. Steady-state plasma digitoxin concentrations did not appear to change. Therefore, monitoring of plasma digoxin levels may be indicated in patients receiving similar combination chemotherapy regimens. The utilization of digitoxin for such patients may be considered as an alternative.

Gentamicin

An *in vitro* interaction study between gentamicin and cytarabine showed a cytarabine related antagonism for the susceptibility of *K. pneumoniae* strains. This study suggests that in patients on cytarabine being treated with gentamicin for a *K. pneumoniae* infection, the lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.

Fluorocytosine

Clinical evidence showed possible inhibition of fluorocytosine efficacy therapy with cytarabine. This may be due to potential competitive inhibition of its uptake.

Methotrexate

Intravenous cytarabine given concomitantly with intrathecal methotrexate may increase the risk of severe neurological adverse reactions such as headache, paralysis, coma and stroke like episodes (see Section 4.4 Special Warnings and Precautions for Use).

4.6 Fertility, Pregnancy and Lactation

Women of Childbearing potential/Contraception in Males and Females

Due to the potential for genotoxicity, advise female patients of reproductive potential to use highly effective contraception during treatment and for 6 months after the last dose of cytarabine.

Due to the potential for genotoxicity, advise male patients with female partners of reproductive potential to use highly effective contraception during treatment and for 3 months after the last dose of cytarabine.

Use in pregnancy

There are no studies on the use of cytarabine in pregnant women. Cytarabine is known to be teratogenic in some animal species (see Section 5.3 Preclinical Safety Data). Use of this drug in women who are or who may become pregnant should be undertaken only after due consideration of potential benefit and potential hazard to both mother and child. Women of childbearing potential should be advised to avoid becoming pregnant.

Normal infants have been born to mothers exposed to cytarabine during pregnancy (alone or in combination with other drugs); some of these infants were premature or of low birthweight. Some of the normal infants were followed up at ages ranging from six weeks to seven years following exposure, and showed no abnormalities. One apparently normal infant died at 90 days of gastroenteritis.

Congenital abnormalities have been reported, particularly when the fetus has been exposed to systemic therapy with cytarabine during the first trimester. These include upper and lower distal limb defects, and extremity and ear deformities.

Reports of pancytopenia, leukopenia, anemia, thrombocytopenia, electrolyte abnormalities, transient eosinophilia, increased IgM levels and hyperpyrexia, sepsis and death have occurred during the neonatal period to infants exposed to cytarabine *in utero*. Some of these infants were also premature.

Therapeutic abortions have been done in pregnant women on cytarabine. Normal fetuses have been reported while other reported fetal effects included enlarged spleen and Trisomy C chromosome abnormality in the chorionic tissue. Because of the potential for abnormalities with cytotoxic therapy, particularly during the first trimester, a patient who is or who may become pregnant while on cytarabine should be apprised of the potential risk to the fetus and the advisability of pregnancy continuation. There is a definite, but considerably reduced risk if therapy is initiated during the second or third trimester. Although normal infants have been delivered to patients treated all three trimesters of pregnancy, follow-up of such infants would be advisable.

Benzyl alcohol which is contained in the diluent can cross the placenta (see Section 4.4 Special Warnings and Precautions for Use).

Breastfeeding

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cytarabine, a decision should be made whether to discontinue nursing for the duration of cytarabine therapy and for at least one week after the last dose or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on Ability to Drive and Use Machines

The effect of cytarabine on the ability to drive or use machinery has not been systematically evaluated.

4.8 Undesirable Effects

Summary of the safety profile (see also Section 4.4 Special Warnings and Precautions for Use).

Blood and lymphatic system disorders

Because cytarabine is a bone marrow suppressant, anemia, leukopenia, thrombocytopenia, megaloblastosis and reduced reticulocytes can be expected as a result of its administration. The

severity of these reactions is dose and schedule dependent. Cellular changes in the morphology of bone marrow and peripheral smears can be expected.

Following 5-day constant infusions or acute injections of 50 mg/m^2 to 600 mg/m^2, white cell depression follows a biphasic course. Regardless of initial count, dosage level, or schedule, there is an initial fall starting the first 24 hours with a nadir at days 7-9. This is followed by a brief rise which peaks around the twelfth day. A second and deeper fall reaches nadir at days 15-24. Then there is rapid rise to above baseline in the next 10 days. Platelet depression is noticeable at 5 days with a peak depression occurring between days 12-15. Thereupon, a rapid rise to above baseline occurs in the next 10 days.

Infections and infestations

Viral, bacterial, fungal, parasitic, or saprophytic infections, in any location in the body, may be associated with the use of cytarabine alone or in combination with other immunosuppressive agents following immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild, but can be severe and at times fatal.

Musculoskeletal and connective tissue disorders

The Cytarabine Syndrome

A cytarabine syndrome has been described by Castleberry. It is characterized by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6-12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are deemed treatable, corticosteroids should be contemplated as well as continuation of therapy with cytarabine.

The reported adverse reactions are listed below by MedDRA System Organ Class and by frequency. Frequencies are defined as: Very common (≥10%), Common (≥1%, <10%), Uncommon (≥0.1%, <1%), Rare (≥0.01%, <0.1%), and Frequency not known (cannot be estimated from available data).

Adverse Reactions Table (Conventional and High Dose Therapy)

Infections and Infestations:	
Very common	Sepsis, pneumonia, infection[a]
Frequency not known	Injection site cellulitis

Blood and Lymphatic System Disorders:	
Very common	Bone marrow failure, thrombocytopenia, anaemia, anaemia megaloblastic, leukopenia, reticulocyte count decreased
Immune System Disorders:	
Frequency not known	Anaphylactic reaction, allergic oedema
Metabolism and Nutrition Disorders:	
Frequency not known	Decreased appetite
Nervous System Disorders:	
Frequency not known	Neurotoxicity, neuritis, dizziness, headache
Eye Disorders:	
Frequency not known	Conjunctivitis[b]
Cardiac Disorders:	
Frequency not known	Pericarditis, sinus bradycardia
Vascular Disorders:	
Frequency not known	Thrombophlebitis
Respiratory, Thoracic and Mediastinal Disorders:	
Frequency not known	Dyspnoea, oropharyngeal pain
Gastrointestinal Disorders:	
Very common	Stomatitis, mouth ulceration, anal ulcer, anal inflammation, diarrhoea, vomiting, nausea, abdominal pain
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
Musculoskeletal, Connective Tissue and Bone Disorders:	
Very common	Cytarabine syndrome
Renal and Urinary Disorders:	
Frequency not known	Renal impairment, urinary retention
General Disorders and Administration Site Conditions:	

Very common	Pyrexia
Frequency not known	Chest pain, injection site reaction[c]
Investigations:	
Very common	Biopsy bone marrow abnormal, blood smear test abnormal

[a]May be mild, but can be severe and at times fatal.

[b]May occur with rash and may be hemorrhagic with high dose therapy.

[c]Pain and inflammation at subcutaneous injection site.

Adverse reactions reported in association with high dose therapy (see also Section 4.4 Special Warnings and Precautions for Use) are included in the following table:

Adverse Reactions Table (High Dose Therapy)

Infections and Infestations:	
Frequency not known	Liver abscess
Psychiatric Disorders:	
Frequency not known	Personality change[a]
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[b]
Respiratory, Thoracic and Mediastinal Disorders:	
Very common	Acute respiratory distress syndrome, pulmonary oedema
Gastrointestinal Disorders:	
Common	Necrotising colitis
Frequency not known	Gastrointestinal necrosis, gastrointestinal ulcer, pneumatosis intestinalis, peritonitis
Hepatobiliary Disorders:	
Frequency not known	Liver injury, hyperbilirubinaemia
Skin and Subcutaneous Tissue Disorders:	
Common	Skin exfoliation

[a] Personality change was reported in association with cerebral and cerebellar dysfunction.

[b] With subsequent death.

Other Adverse Reactions

A diffuse interstitial pneumonitis without clear cause that may have been related to cytarabine was reported in patients treated with experimental intermediate doses of cytarabine (1 g/m^2) with and without other chemotherapeutic agents (meta-AMSA, daunorubicin, VP-16).

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary edema and a radiographically pronounced cardiomegaly has been reported following experimental high dose therapy with cytarabine used for the treatment of relapsed leukemia; fatal outcome has been reported.

Intrathecal Use

The most frequently reported reactions after intrathecal administration were nausea, vomiting and fever; these reactions are mild and self-limiting. Paraplegia has been reported. Necrotizing leukoencephalopathy with or without convulsion has been reported; in some cases patients had also been treated with intrathecal methotrexate and/or hydrocortisone, as well as by central nervous system radiation. Isolated neurotoxicity has been reported. Blindness occurred in two patients in remission whose treatment had consisted of combination systemic chemotherapy, prophylactic central nervous system radiation and intrathecal cytarabine.

4.9 Overdose

There is no antidote for overdosage of cytarabine. Doses of 4.5 g/m^2 by intravenous infusion over 1 hour every 12 hours for 12 doses have caused an unacceptable increase in irreversible CNS toxicity and death.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Cytarabine, a pyrimidine nucleoside analogue, is an antineoplastic agent which inhibits the synthesis of deoxyribonucleic acid. It also has antiviral and immunosuppressant properties. Detailed studies on the mechanism of cytotoxicity *in vitro* suggest that the primary action of cytarabine is inhibition of deoxycytidine synthesis, although inhibition of cytidylic kinases and incorporation of the compound into nucleic acids may also play a role in its cytostatic and cytocidal actions.

5.2 Pharmacokinetic Properties

Cytarabine is deaminated to arabinofuranosyl uracil in the liver and kidneys. After intravenous administration to humans, only 5.8% of the administered dose is excreted unaltered in urine within 12-24 hours; 90% of the dose is excreted as the deaminated product. Cytarabine appears to be metabolized rapidly, primarily by the liver and perhaps by the kidney. After single high intravenous doses, blood levels fall to unmeasurable levels within 15 minutes in most patients. Some patients have indemonstrable circulating drug as early as 5 minutes after injection.

5.3 Preclinical Safety Data

The major dose-limiting toxicity of cytarabine observed in all tested species is myelosuppression, manifested by megaloblastosis, reticulocytopenia, leukopenia, and thrombocytopenia. Other target organs include liver, kidney, and brain. Extensive chromosomal damage, including chromatoid breaks have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported. Cytarabine is embryotoxic and teratogenic and produced peri- and post-natal toxicity in various species. No formal fertility studies have been reported however sperm head abnormalities were observed following cytarabine treatment in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium chloride, water for injection BP.

6.2 Incompatibilities

Drug Incompatibilities

Cytarabine has been known to be physically incompatible with heparin, insulin, 5-fluorouracil, penicillins such as oxacillin and pen-G, and methylprednisolone sodium succinate.

Cytarabine must not be mixed with other medicinal products except those mentioned in Section 4.2 Posology and Method of Administration. Compatibility must be assured before mixing with any other substance.

6.3 Shelf Life

Please see details on the carton.

Stability in infusion solutions

Chemical and physical stability studies of cytarabine have demonstrated that cytarabine is stable for

seven days at room temperature when admixed at 0.5 mg/mL in glass IV bottles and plastic IV bags with: water for injection; 5% Dextrose injection; and 0.9% Sodium Chloride injection solutions. Also when similarly admixed at 8-32 mg/mL in glass IV bottles and plastic IV bags, cytarabine is stable for seven days at room temperature. -20ºC, and 4ºC in 5% Dextrose Injection; 5% Dextrose in 0.2% Sodium Chloride Injection; and, in 0.9% Sodium Chloride Injection Solutions.

Cytarabine is stable at room temperature at a concentration of 2 mg/mL in the presence of KCl equivalent to 50 meq/500 mL in Dextrose 5% in water and 0.9% Sodium Chloride for up to eight days.

Cytarabine is also stable at room temperature and at refrigerated temperature (8ºC) at a concentration of 0.2-1.0 mg/mL in the presence of Sodium Bicarbonate equivalent to 50 meq/L in Dextrose 5% in Water or Dextrose 5% in 0.2% Sodium Chloride for seven days in Travenol glass bottles or Viaflex bags.

Cytarabine injection, and the infused solutions prepared therefrom, contain(s) no antimicrobial agents. Therefore, it is recommended that further dilution be effected immediately prior to use and infusion be commenced 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 15ºC-25ºC and protect from light.

7. MARKETING AUTHORIZATION HOLDER

Pfizer (Thailand) Limited., Thailand.

8. MARKETING AUTHORIZATION NUMBERS

CYTOSAR CS (20 mg/mL) Reg. No. 1C 209/47
CYTOSAR CS (100 mg/mL) Reg. No. 1C 2/50

9. DATE OF AUTHORIZATION

27 August 2004, 12 January 2007

10. DATE OF REVISION OF THE TEXT

27 June 2022

Warning (Based on the Ministry of Public Health's Announcement)

This drug may cause serious harm, should be used under the supervision of a physician.

LPD Revision No.: 9.0

LPD Date: June 27, 2022

Country: Thailand