Cytarabine Injection BP

CYTOSAR®

1. GENERIC NAME

Cytarabine Injection BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cytosar is available as solution for injection containing Cytarabine I.P. 20 mg/ml and 100 mg/ml.

For full list of excipients, see section 7

All strengths/presentations mentioned in this document might not be available in the market.

3. DOSAGE FORM AND STRENGTH

Sterile Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cytarabine is indicated primarily for induction and maintenance of remission in acute myelocytic leukaemia of both adults and children. It has also been found to be useful in the treatment of other leukaemias such as acute lymphocytic leukaemia, chronic myelocytic leukaemia (blast phase) and erythroleukaemia. Cytarabine may be used alone or in combination with other antineoplastic agents, the best results are often obtained with combination therapy.

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

Remissions induced by cytarabine not followed by maintenance treatment have been brief. Maintenance therapy has extended these and provided useful and comfortable remissions with relatively little toxicity.

Cytarabine has been used intrathecally in meningeal leukaemia.

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

4.2 Posology and Method of Administration

Cytarabine may be administered by intravenous injection or infusion, or subcutaneously. It has been administered intrathecally as a special application.

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.

Dose regimens are usually at the discretion of the attending physician. Clinical and haematological responses and tolerance vary between patients and a dose which gives optimal therapeutic effect with minimum toxicity should be used.

Normal Adult Dosage, Single Agent Therapy

Doses of up to 200 mg/m^2 daily as a continuous intravenous infusion for five days (120 hours) repeated at approximately two weekly intervals have been used. Modification must be made based on results of daily haematological monitoring.

After each five day treatment, drug therapy should be withdrawn to allow for bone marrow recovery.

Dilutions of cytarabine should be made in Glucose 5% or Sodium Chloride 0.9% Intravenous Infusions to concentrations as low as 0.1 mg/mL. In order to reduce any microbiological hazard it is recommended that dilution should be effected immediately prior to use and infusion commenced as soon as practicable after preparation of the admixture. Infusion should be completed within 24 hours of preparation and any residue discarded. Any storage should be between 2-8°C, protected from light.

Maintenance of Acute Myelocytic Leukaemia in Adults

Maintenance programs are generally modifications of induction programs. Similar schedules of drug therapy to those used for induction are normally employed. Most programs have a greater interval between courses of therapy during remission maintenance.

Induction and Maintenance of Acute Myelocytic Leukaemia (AML) in Children

Childhood AML has been shown to respond better than adult AML given similar regimes. Where the adult dosage is given in terms of body weight or surface area, the paediatric dosage may be calculated on the same basis, being adjusted on the consideration of such factors as age, body weight or body surface area.

Conditions Requiring Dosage Adjustment

Myelosuppression

The dose of cytarabine should be modified if signs of severe myelosuppression appear, e.g. consideration of discontinuation of the drug if the polymorphonuclear granulocyte count falls below 1 x 10^9 L or the platelet count falls below 50 x 10^9 L.

Combination Therapy

Dosage modifications may have to be made when cytarabine is used in combination with other myelosuppressive drugs. Before instituting a program of combined therapy, the physician should be familiar with the adverse effects, precautions, contraindications and warnings applicable to all the drugs in the program.

Intrathecal Use in Meningeal Leukaemia

Cytarabine has been used intrathecally in acute leukaemia 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. It has been 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. 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 paediatric 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.

Incompatibilities

Cytarabine must not be mixed with other medicinal products except those mentioned above. Cytarabine has been known to be physically incompatible with heparin, insulin, fluorouracil, penicillins such as oxacillin and penicillin G sodium, and methylprednisolone sodium succinate.

Handling Precautions

As with all antineoplastic agents, trained personnel should prepare Cytarabine Injection. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling cytarabine. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as cytarabine.

Luer-Lock fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.

Items used to prepare cytarabine, or articles associated with body waste, should be disposed of by placing in a double sealed polythene bag and incinerating at 1100°C.

For information on Spills and Disposal, see section 8.4 Storage and handing instructions.

4.3 Contraindications

Known hypersensitive to cytarabine.

4.4 Special Warnings and Precautions for Use

Cytarabine should be administered only under constant supervision by physicians experienced in therapy with cytotoxic agents and only when the potential benefits of cytarabine therapy outweigh the possible risks. 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. Appropriate facilities should be available for adequate management of complications should they arise.

The main toxic effect of cytarabine is bone marrow suppression with leukopenia, thrombocytopenia and anaemia. Less serious toxicity includes nausea, vomiting, diarrhoea and abdominal pain, oral ulceration, and hepatic dysfunction.

Myelosuppression

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 should undergo close medical supervision including daily assessment of leukocyte and platelet levels. Bone marrow examinations should be performed frequently after blasts have disappeared from the peripheral blood. Facilities should be available for management of complications, possibly fatal, of bone marrow suppression (infection resulting

from granulocytopenia and other impaired body defences and haemorrhage secondary to thrombocytopenia). Consider suspending or modifying therapy when drug-induced marrow depression has resulted in a platelet count under 50 x 10^9 L or a polymorphonuclear granulocyte count under 1 x 10^9 L. 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 (on successive bone marrow studies). Patients whose drug is withheld until "normal" peripheral blood values are attained may escape from control.

Intrathecal Use

Cytarabine given intrathecally may cause systemic toxicity and careful monitoring of the hematopoietic system is indicated. Modification of the anti-leukemia therapy may be necessary. Major toxicity is rare (See section **4.2**). When cytarabine is administered both intrathecally and intravenously within a few days, there is an increased risk of spinal cord toxicity.

Hepatic and/or Renal Function

The liver is the main site of inactivation of cytarabine and the normal dosage regimen should be used with caution in patients with pre-existing liver dysfunction or poor renal function. In particular, patients with renal or hepatic function impairment may have a higher likelihood of CNS toxicity after high-dose treatment with cytarabine.

Monitoring

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.

Hyperuricaemia

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.

Anaphylaxis

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.

Acute Pancreatitis

Acute pancreatitis has been reported to occur in patients being treated with cytarabine who have had prior treatment with L-asparaginase.

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.

Vomiting

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.

Experimental Doses

Severe, and at times fatal, CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following some experimental dose 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); usually reversible cerebral and cerebellar dysfunction (including personality changes, somnolence and coma); severe gastrointestinal ulceration(including pneumatosis cystoides intestinalis leading to peritonitis); sepsis and liver abscess; pulmonary oedema, liver damage with increased hyperbilirubinemia; bowel necrosis; and necrotizing colitis.

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

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 neurologic disorders.

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

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 Drug Interactions

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**).

Cytarabine has been reported to inhibit the cellular uptake of methotrexate, thus reducing its effectiveness. Conversely, methotrexate has been reported to reduce the cellular activity of cytarabine. These factors should be taken into consideration if the two drugs are used concomitantly.

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 in one patient showed possible inhibition of fluorocytosine efficacy therapy with cytarabine. This may be due to potential competitive inhibition of its uptake.

4.6 Use in Special populations

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.

Effects on fertility

No data available

Use in Pregnancy – Pregnancy Category D

Cytarabine is known to be teratogenic in some animal species and its use in pregnant women is not recommended. Cytarabine should only be used in women of childbearing potential if the expected benefits outweigh the risks of therapy and adequate contraception is used.

A review of the literature has shown 32 reported cases where cytarabine was given during pregnancy, either alone or in combination with other cytotoxic agents: Eighteen normal infants were delivered. Four of these had first trimester exposure. Five infants were premature or of low birth weight. Twelve of the 18 normal infants were followed up at ages ranging from 6 weeks to 7 years, and showed no abnormalities. One apparently normal infant died at 90 days of gastroenteritis.

Two cases of congenital abnormalities have been reported, one with upper and lower distal limb defects, and the other with extremity and ear deformities. Both of these cases had first trimester exposure. There were seven infants with various problems in the neonatal period, including pancytopenia; transient depression of WBC, haematocrit or platelets; electrolyte abnormalities; transient eosinophilia; and one case of increased IgM levels and hyperpyrexia possibly due to sepsis. Six of the seven infants were also premature. The child with pancytopenia died at 21 days of sepsis.

Therapeutic abortions were done in five cases. Four fetuses were grossly normal, but one had an enlarged spleen and another showed 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.

Use in lactation

It is not known whether cytarabine is excreted in breast milk, so breast feeding should be discontinued during cytarabine therapy, and for at least one week after the last dose, in lactating women.

4.7 Effects on Ability to Drive and Use Machines

The effect of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable Effects

Summary of Safety Profile (See also section 4.4)

Haematological

Myelosuppression: cytarabine is a potent bone marrow suppressant, anaemia, leukopenia, thrombocytopenia, megaloblastosis and reduced reticulocytes can be expected. 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.

Gastrointestinal

Nausea and vomiting are common and are more severe following rapid intravenous infusion.

Cytarabine (Ara-C) syndrome

A cytarabine syndrome characterized by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise has been reported. 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.

Infectious Complications

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.

Tabulated Summaries of Adverse Effects

The reported adverse reactions are listed below by 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).

Table 1: Adverse Effects Table	
Infections and Infestations	
Very common	Sepsis, pneumonia, infection[a]
Uncommon	Injection site cellulitis
Blood and Lymphatic System Disorders	
Very common	Bone marrow failure, thrombocytopenia, anaemia, anaemia megaloblastic, leukopenia, reticulocyte count decreased
Immune System Disorders	
Uncommon	Anaphylactic reaction[b], allergic oedema
Metabolism and Nutrition Disorders	
Common	Anorexia
Nervous System Disorders	
Uncommon	Neurotoxicity, neuritis, dizziness, headache
Eye Disorders	
Uncommon	Conjunctivitis[c]
Cardiac Disorders	
Frequency not known	Pericarditis, sinus bradycardia
Vascular Disorders	
Common	Bleeding (all sites), thrombophlebitis
Respiratory, Thoracic and Mediastinal Disorders	
Uncommon	Sore throat, shortness of breath
Gastrointestinal Disorders	
Very common	Stomatitis, mouth ulceration, anal ulcer, anal inflammation, diarrhoea, vomiting[d], nausea[d], abdominal pain
Uncommon	Oesophagitis, oesophageal ulceration, bowel necrosis
Frequency not known	Pancreatitis
Hepatobiliary Disorders	

Very common	Hepatic function abnormal
Uncommon	Jaundice
Skin and Subcutaneous Tissue Disorders	
Very common	Alopecia, rash
Common	Skin ulceration
Uncommon	Urticaria, pruritus, ephelides
Frequency not known	Toxic erythema of chemotherapy[e]
Musculoskeletal, Connective Tissue and Bone Disorders	
Very common	Cytarabine syndrome
Renal and Urinary Disorders	
Uncommon	Renal dysfunction, urinary retention
General Disorders and Administration Site Conditions	
Very common	Pyrexia
Uncommon	Chest pain
Frequency not known	Injection site reaction[f]
Investigations	
Very common	Biopsy bone marrow abnormal, blood smear test abnormal

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

[b] Resulting in cardiopulmonary arrest has been reported following intravenous administration

[c] May occur with rash and may be haemorrhagic with high dose therapy

[d] Nausea and vomiting are most frequent following rapid intravenous injection

[e] Toxic erythema of chemotherapy includes the terms hidradenitis, palmar-plantar erythrodysaesthesia syndrome, red ear syndrome, toxic erythema of chemotherapy.

[f] Pain and inflammation at subcutaneous injection site.

Table 2: Adverse Effects Table (Experimental Dose Therapy) (see Section 4.4)	
Infections and Infestations	
Frequency not known	Sepsis, 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	Haemorrhagic conjunctivitis, corneal disorder
Cardiac Disorders	
Frequency not known	Cardiomyopathy[b], sinus bradycardia
Respiratory, Thoracic and Mediastinal Disorders	
Very common	Acute respiratory distress syndrome, pulmonary oedema
Gastrointestinal Disorders	
Common	Necrotising colitis
Frequency not known	Bowel necrosis, gastrointestinal ulcer, pneumatosis intestinalis, peritonitis

Hepatobiliary Disorders	
Frequency not known	Liver injury, hyperbilirubinaemia
Skin and Subcutaneous Tissue Disorders	
Common	Skin rash leading to desquamation, alopecia
[a] Personality change was reported in association with cerebral and cerebellar dysfunction. [b] With subsequent death	

Other Adverse Reactions

Experimental Dose Schedule

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

Intermediate Dose Schedule

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).

Intrathecal Administration

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. Delayed progressive ascending paralysis resulting in death has been reported in children with acute myelogenous leukaemia (AML) following intrathecal and intravenous cytarabine at conventional doses in combination with other drugs.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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.

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 has caused an unacceptable increase in irreversible CNS toxicity and death. Symptoms of overdose include nausea, vomiting, diarrhoea, ulceration and bleeding of the gastrointestinal tract, myelosuppression, severe skin rash, CNS toxicity (including

cerebral and cerebellar dysfunction), cardiac disorders, pulmonary and corneal toxicity, fever, myalgia, bone pain, chest pain and conjunctivitis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

The exact mechanism(s) of action of cytarabine has not been fully elucidated, however it appears to act through DNA synthesis inhibition. Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. Extensive chromosomal damage, including chromatoid breaks, have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported. Deoxycytidine prevents or delays (but does not reverse) the cytotoxic activity.

Cell culture studies have shown an antiviral effect. However, efficacy against *herpes zoster* or smallpox could not be demonstrated in controlled clinical trials.

5.2. Pharmacodynamic Properties

Cytarabine is converted intracellularly to an active metabolite (cytarabine triphosphate) which inhibits DNA synthesis. The enzyme responsible for this conversion is deoxycytidine kinase which is found predominantly in the liver and possibly the kidney. Cytarabine is inactivated by the enzyme cytidine deaminase found in the intestine, kidney and liver. The ratio of the activating enzyme (deoxycytidine kinase) to the inactivating enzyme (cytidine deaminase) in cells, determines the susceptibility of the tissue to the cytotoxic effects of cytarabine. Tissues with a high susceptibility have high levels of the activating enzyme. Cytarabine has no effect on non-proliferating cells, or on proliferating cells unless in the S or DNA synthesis phase. Thus, cytarabine is a cell cycle phase-specific antineoplastic drug.

Immunosuppressive Action

Cytarabine is capable of obliterating immune responses in man during administration with little or no accompanying toxicity. Suppression of antibody responses to *E.coli-V1* antigen and tetanus toxoid have been demonstrated. This suppression was obtained during both primary and secondary antibody responses.

Cytarabine also suppressed the development of cell-mediated immune responses such as delayed hypersensitivity skin reaction to dinitrochlorobenzene. However, it had no effect on already established delayed hypersensitivity reactions.

Following 5-day courses of intensive therapy with cytarabine the immune response was suppressed, as indicated by the following parameters: macrophage ingress into skin windows; circulating antibody response following primary antigenic stimulation; lymphocyte blastogenesis with phytohaemaglutinin. A few days after termination of therapy there was a rapid return to normal.

Clinical trials

No data available

5.3 Pharmacokinetic Properties

Absorption

Orally, less than 20% of a dose of cytarabine is absorbed from the gastrointestinal tract and is ineffective by this route. Subcutaneously or intramuscularly, tritium labelled cytarabine produces peak plasma concentrations of radioactivity within 20 - 60 minutes and are considerably lower than those attained after intravenous administration. Continuous intravenous infusions produce relatively constant plasma levels in 8 - 24 hours.

Distribution

Cytarabine is widely distributed into tissues including liver, plasma and peripheral granulocytes. Cytarabine crosses the blood-brain-barrier to a limited extent and is thought to cross the placental barrier. It is not known if cytarabine is distributed into milk.

Cerebrospinal fluid levels of cytarabine are low in comparison to plasma levels after single intravenous injection. However, in one patient in whom cerebrospinal levels were examined after 2 hours of constant intravenous infusion, levels approached 40 percent of the steady state plasma level. With intrathecal administration, levels of cytarabine in the cerebrospinal fluid declined with a first order half-life of about 2 hours. Because cerebrospinal fluid levels of deaminase are low, little conversion to ara-U was observed.

Metabolism

Intravenous doses of cytarabine exhibit a biphasic elimination, with an initial distribution half-life of about 10 minutes during which time a major portion of the drug is metabolised in the liver to the inactive metabolite uracil arabinoside. The secondary elimination half-life is longer, approximately 1 - 3 hours. Metabolism occurs also in the kidneys, gastrointestinal mucosa, granulocytes and other tissues.

Excretion

Cytarabine is mainly excreted via the kidney with 70 - 80% of a dose administered by any route appearing in the urine within 24 hours; approximately 90% as the metabolite and 10% as unchanged drug.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Genotoxicity

No data available.

Carcinogenicity

No data available.

7. DESCRIPTION

Cytarabine Injection BP is a clear, colourless or pale-yellow, sterile, isotonic, preservative-free solution containing Cytarabine I.P. 100 mg in 5 ml, 1000 mg in 10 ml. The solutions are packed in polypropylene (medical grade) vials, closed with either ethylene propylene diene monomer (EPDM) or halobutyl (Fluro Tec Plus-faced) rubber stoppers and sealed with aluminium crimps and plastic flip-off tops.

Cytarabine Injection 20 mg/ml

Sodium Chloride
Hydrochloric Acid
Sodium Hydroxide
Water for Injection

Cytarabine Injection 100 mg/ml

Hydrochloric Acid
Sodium Hydroxide
Water for Injection

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

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

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

8.2 Shelf-life

Solution for injection:
18 months.

8.3 Packaging information

Cytarabine Injection BP 100 mg in 5 mL - 1 sterile cytosafe vial
Cytarabine Injection BP 1000 mg in 10 mL - 1 sterile cytosafe vial

8.4. Storage and handing instructions

Store between 15ºC and 25ºC.
Do not refrigerate.
Protect from light.

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, -20°C, and 4°C 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 (8˚C) 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.

Special Precautions for Disposal of a Used Medicinal Product or Waste Materials Derived from Such Medicinal Product and Other Handling of the Product

Single use only. Discard unused portion.

As with all antineoplastic agents, trained personnel should prepare Cytarabine Injection. This should be performed in a designated area (preferably in a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling Cytarabine. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as Cytarabine.

Luer-Lock fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation. Items used to prepare Cytarabine, or articles associated with body waste, should be disposed of by placing in a double sealed polythene bag and incinerating at 1100°C.

If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with a suitable material such as absorbent towel or adsorbent granules. Spills may also be treated with 5% Sodium hypochlorite. Collect up absorbent/adsorbent material and other debris from spill and place in a leak proof plastic container and label accordingly.

Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled 'CYTOTOXIC WASTE FOR INCINERATION AT 1100°C'. Waste material should be incinerated at 1100°C for at least 1 second. Cleanse the remaining spill area with copious amounts of water.

9. PATIENT COUNSELLING INFORMATION

Cytosar may cause bone marrow suppression that may lower red blood cells, white blood cells and platelet count, increasing the risk of bleeding. Patients need to be counselled regarding unusual bruising, bleeding gums, nosebleeds, blood in urine or stools, or prolonged bleeding from cuts.

Reduction in blood counts due to Cytosar may make the patients more likely to develop infections. 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. Some infections can become serious and may require urgent medical attention.

Patients need to be counselled on need for regular blood tests to monitor their blood cell counts, liver function, and kidney function during treatment.

Nausea, vomiting, abdominal discomfort, diarrhoea, and mouth ulcers can occur during treatment. Some patients may experience a reaction called "Cytarabine Syndrome" within a few hours after treatment. Symptoms may include fever, muscle aches, bone pain, rash, conjunctivitis, chest discomfort, and general feeling of illness.

Patients need to be counselled that they should not receive any live vaccines during treatment with Cytosar unless advised by the treating physician.

Cytosar may harm an unborn baby and its use in pregnant women is not recommended. Cytarabine should only be used in women of childbearing potential if the expected benefits outweigh the risks of therapy and adequate contraception is used. It is not known whether Cytarabine is excreted in breast milk, so breast feeding should be discontinued during cytarabine therapy, and for at least one week after the last dose, in lactating women.

10. DETAILS OF MANUFACTURER

MANUFACTURED BY

M/s. Bridgewest Perth Pharma Pty. Ltd., 15 Brodie Hall Drive, Bentley, Western Australia 6102, Australia

IMPORTED AND MARKETED IN INDIA BY:

Pfizer Products India Private Limited, The Capital- B Wing, 1802, 18th Floor, Plot No. C-70, G Block, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

FF-328-6803 dated 18-Mar-2024* (* The license is renewed every 3 years as per regulations).

12. DATE OF REVISION

June 2026