AUSTRALIAN PRODUCT INFORMATION – DBL™ CYTARABINE INJECTION (Cytarabine)

1. NAME OF THE MEDICINE

Cytarabine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Cytarabine Injection (100 mg/mL) is a clear, colourless sterile solution of cytarabine in water for injections also contains hydrochloric acid and sodium hydroxide for pH adjustment. It is presented in ONCO-TAIN® vials containing 1000 mg/10 mL or 2000 mg/20 mL of cytarabine solution. The solution does not contain any antimicrobial preservative.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

DBL Cytarabine Injection 100 mg/mL is a clear, colourless sterile solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cytarabine may be used alone or in combination with other chemotherapeutic agents. It is indicated for induction of remission of leukaemia, particularly for acute myeloid leukaemia, in adults and children.

Cytarabine has been used for remission induction in acute lymphocytic leukaemia, chronic myeloid leukaemia and erythroleukaemia; and in the treatment and maintenance therapy of meningeal leukaemia and other meningeal neoplasms.

4.2 Dose and Method of Administration

Dosage

Dosage of cytarabine must be based on the clinical and haematological response and tolerance of the patient so as to obtain optimum therapeutic results with minimum adverse effects. Even though higher total doses of cytarabine can be given by IV injection compared to continuous IV infusion with similar haematologic toxicity, the most effective dosage schedule and method of administration are yet to be established. Moreover, cytarabine is often used in combination with other cytotoxic drugs, thereby necessitating dose modification of cytarabine and other chemotherapeutic agents, and the method as well as the sequence of administration.

Following is an outline of dosage schedules for cytarabine therapy as reported in the literature.

Dosage schedules:

Single-Drug Therapy in induction remission in adults with Acute Myelocytic Leukaemia:

Cytarabine 200 mg/m^2 daily by continuous IV infusion over 24 hours for 5 days (120 hours) - total dose 1000 mg/m^2. The course is repeated approximately every 2 weeks. Modifications based on haematologic response must be made.

After each five day treatment, drug therapy should be withdrawn to allow for bone marrow recovery.

Cytarabine combination therapy:

Before a combined chemotherapy protocol is instituted, the clinician should be familiar with current literature, precautions, contraindications, adverse reactions and warnings applicable to all the drugs involved in the protocol.

Cytarabine, Daunorubicin
Cytarabine: 100 mg/m^2/day, continuous IV infusion (days 1-7)
Daunorubicin: 45 mg/m^2/day, IV push (days 1-3)

Additional courses (complete or modified) as required at 2-4 week intervals if leukaemia is persistent.

Cytarabine, Thioguanine, Daunorubicin
Cytarabine: 100 mg/m^2/day, IV infusion over 30 minutes every 12 hours (days 1-7)
Thioguanine: 100 mg/m^2, orally every 12 hours (days 1-7)
Daunorubicin: 60 mg/m^2/day, IV infusion (days 5-7)

Additional courses (complete or modified) as required at 2-4 week intervals if leukaemia is persistent.

Cytarabine, Doxorubicin
Cytarabine: 100 mg/m^2/day, continuous IV infusion (days 1-10)
Doxorubicin: 30 mg/m^2/day, IV infusion over 30 minutes (days 1-3)

Additional courses (complete or modified) as required at 2-4 week intervals if leukaemia is persistent.

Cytarabine, Doxorubicin, Vincristine, Prednisolone
Cytarabine: 100 mg/m^2/day, continuous IV infusion (days 1-7)
Doxorubicin: 30 mg/m^2/day, IV infusion (days 1-3)
Vincristine: 1.5 mg/m^2/day, IV infusion (days 1, 5)
Prednisolone: 40 mg/m^2/day, IV infusion every 12 hours (days 1-5)

Additional courses (complete or modified) as required at 2-4 week intervals if leukaemia is persistent.

Cytarabine, Daunorubicin, Thioguanine, Prednisone, Vincristine
Cytarabine: 100 mg/m^2/day, IV every 12 hours (days 1-7)
Daunorubicin: 70 mg/m^2/day, IV infusion (days 1-3)

Thioguanine: 100 mg/m^2 orally every 12 hours (days 1-7)
Prednisone: 40 mg/m^2/day, orally (days 1-7)
Vincristine: 1 mg/m^2/day, IV infusion (days 1,7)

Additional courses (complete or modified) as required, 2-4 week intervals, if leukaemia is persistent.

Maintenance of Acute Myelocytic Leukaemia (AML) 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 regimens. 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.

Acute Lymphocytic Leukaemia (ALL):

Dosage schedules used in ALL are normally similar to those used in AML with some modifications.

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 (see Section 4.8 Adverse effects (undesirable effects)).

Dosage modification:

Suspension or modification of cytarabine therapy should be considered at the appearance of signs of serious haematologic depression, for example, if the polymorphonuclear granulocyte count falls below 1000/mm^3 or the platelet count falls below 50,000/mm^3. Such guidelines may be modified, depending on signs of toxicity in other systems and on the speed of fall in levels of formed blood elements. Therapy should be recommended when definite signs of bone marrow recovery appear and the above granulocyte and platelet levels are attained. If therapy is withheld until peripheral counts of blood elements return to normal, cytarabine may be ineffective.

DBL Cytarabine Injection is a ready to use solution with a concentration of 100 mg/mL. It is suitable for intravenous use and in small volumes may also be used subcutaneously.

The potency of cytarabine is retained for 24 hours at 25°C in the following IV fluids:

1. Water for Injection
2. Glucose 5% in water
3. Sodium Chloride 0.9%

4. Ringer's injection, lactated

Dilutions of cytarabine should be made in Glucose 5% in water or Sodium Chloride 0.9% Intravenous Infusions to concentrations as low as 0.1 mg/mL. Although stability of cytarabine is well retained for 24 hours in intravenous vehicles noted above, it is recommended that, as with all intravenous admixtures, dilution should be made just prior to administration and the resulting solution used within 24 hours to reduce any microbiological hazard.

Method of Administration

Being orally inactive, cytarabine is administered by a variety of parenteral routes: subcutaneously, intravenously either as a bolus "push" or as a continuous infusion, or intrathecally.

Thrombophlebitis has occurred at the site of drug injection or infusion in some patients. Pain and inflammation at subcutaneous injection sites are rare. Subcutaneous injection sites should be rotated around the areas of body fat: the abdomen, thighs and flank region. The drug is generally well tolerated in most instances.

Higher total doses 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 neoplastic cells to significant levels after rapid injection.

Normal and neoplastic cells appear to respond in almost parallel manner to these two modes of administration and no distinct advantage has been established for either.

Clinical experience to date indicates that success with cytarabine therapy depends more on adeptness in modifying day-to-day dosage to obtain maximum leukaemic cell kill with tolerable toxicity, than on the fundamental treatment protocol selected at the start of therapy. Toxicity necessitating dosage modification almost always occurs.

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 6.6 Special Precautions for Disposal.

4.3 Contraindications

Cytarabine is contraindicated in patients with known hypersensitivity to the drug.

4.4 Special Warnings and Precautions for Use

Cytarabine should only be used 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 and 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 the drug must be kept under close medical supervision. Leukocyte and platelet counts should be performed daily and frequent bone marrow examinations conducted 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 haemopoietic system is indicated. Modification of other anti-leukaemia therapy may be necessary (see Section 4.2 Dose and method of administration). When cytarabine is administered both intrathecally and intravenously within a few days, there is an increased risk of spinal cord toxicity.

Monitoring

Periodic determinations of bone marrow, renal and hepatic function should also 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

Similar to other cytotoxic drugs, hyperuricaemia secondary to rapid lysis of neoplastic cells may occur in patients receiving cytarabine; serum uric acid concentrations should be monitored by the clinician and be prepared to use such supportive and pharmacological 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 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. The severity is less if the solution 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) have been reported following some experimental dose schedules of cytarabine. These reactions include reversible corneal toxicity, and haemorrhagic 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 hyperbilirubinaemia; bowel necrosis; and necrotising colitis.

Severe 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 leukaemia. The outcome of this syndrome can be fatal.

Cases of cardiomyopathy with subsequent death have been reported following experimental high dose therapy with 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 dose cytarabine, daunorubicin and asparaginase have occurred in adult patients with non-lymphocytic leukaemia. Patients treated with high dose cytarabine should be observed for neuropathy since dose schedule alteration 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 experimental high dose therapy than with standard cytarabine treatment programs.

Use in hepatic impairment

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. In particular, patients with hepatic function impairment may have a higher likelihood of CNS toxicity after high-dose treatment with cytarabine.

Use in renal impairment

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 renal dysfunction. In particular, patients with renal function impairment may have a higher likelihood of CNS toxicity after high-dose treatment with cytarabine.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 Interactions with Other Medicines and Other Forms of Interactions

The incidence and severity of haematologic toxicity induced by cytarabine is exacerbated when other myelosuppressive drugs are given concurrently. 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.

Use with care following prior treatment with L-asparaginase (see Section 4.4 Special warnings and precautions for use).

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).

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 utilisation 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.

Flucytosine

Flucytosine should not be administered concomitantly with cytarabine. Cytarabine has been reported to antagonise the antifungal activity of flucytosine by competitive inhibition.

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.

Effects on fertility

No data available.

Use in 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.

Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

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 in 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 human milk. Women should be advised not to breast feed while being treated with cytarabine and for at least one week after the last dose.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Adverse Effects (Undesirable Effects)

Summary of Safety Profile (see also Section 4.4 Special warnings and precautions for use)

Haematological

The major adverse effect of cytarabine is haematologic toxicity. Cytarabine is a potent bone marrow suppressant. Myelosuppression is normally manifested by megaloblastosis, leukopenia, anaemia, reticulocytopenia and thrombocytopenia. Leukopenia follows mainly from granulocyte depression; lymphocytes are minimally affected. The severity of these

adverse effects is dependent on the dose of the drug and schedule of administration. Cellular changes in the morphology of bone marrow and peripheral smears can be expected.

The incidence and severity of haematologic toxicity is minimal after a single intravenous dose of cytarabine, but myelosuppression occurs in almost all patients with daily IV injections or continuous IV infusions of the drug.

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 a 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 may occur in patients on cytarabine therapy, and usually occur more frequently and severely following rapid IV administration as opposed to continuous infusion of the drug.

In one study, cytarabine has been reported to induce severe intestinal toxicity when used in several sequential chemotherapeutic protocols. The mucosal alterations induced were characterised by surface and glandular epithelial atypia, immaturity and necrosis. These were associated with diarrhoea, ileus, abdominal pain, haematemesis and melaena, severe hypokalaemia, hypocalcaemia, a protein-losing enteropathy, transient weight gains and intestinal infections.

Cytarabine (Ara-C) Syndrome

A cytarabine syndrome, characterised by fever, myalgia, bone pain, malaise, maculopapular rash, conjunctivitis, and occasionally chest pain, has been reported. It normally occurs 6-12 hours after administration of the drug; corticosteroids have been shown to be of benefit in the treatment and prevention of the syndrome. If treatment of the symptoms of the syndrome is required, administration of corticosteroids should be considered as well as continuation of cytarabine therapy.

Infectious Complications

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

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	
Sepsis, pneumonia, infection[a]	Very common
Injection site cellulitis	Uncommon
Blood and Lymphatic System Disorders	
Bone marrow failure, thrombocytopenia, anaemia, anaemia megaloblastic, leukopenia, reticulocyte count decreased	Very common
Immune System Disorders	
Anaphylactic reaction[b], allergic oedema	Uncommon
Metabolism and Nutrition Disorders	
Anorexia	Common
Nervous System Disorders	
Neurotoxicity, neuritis, dizziness, headache	Uncommon
Eye Disorders	
Conjunctivitis[c]	Uncommon
Cardiac Disorders	
Pericarditis, sinus bradycardia	Frequency not known
Vascular Disorders	
Bleeding (all sites), thrombophlebitis	Common
Respiratory, Thoracic and Mediastinal Disorders	
Sore throat, shortness of breath	Uncommon
Gastrointestinal Disorders	
Stomatitis, mouth ulceration, anal ulcer, anal inflammation, diarrhoea, vomiting[d], nausea[d], abdominal pain	Very common
Oesophagitis, oesophageal ulceration, bowel necrosis	Uncommon
Pancreatitis, oral inflammation, GI haemorrhage	Frequency not known
Hepatobiliary Disorders	
Hepatic function abnormal	Very common
Jaundice	Uncommon
Skin and Subcutaneous Tissue Disorders	
Alopecia, rash	Very common
Skin ulceration	Common
Urticaria, pruritus, ephelides	Uncommon
Toxic erythema of chemotherapy[e]	Frequency not known
Musculoskeletal, Connective Tissue and Bone Disorders	
Cytarabine syndrome	Very common
Renal and Urinary Disorders	
Renal dysfunction, urinary retention	Uncommon
General Disorders and Administration Site Conditions	
Pyrexia	Very common
Chest pain	Uncommon
Injection site reaction[f]	Frequency not known
Investigations	

Table 1: Adverse Effects Table	
Biopsy bone marrow abnormal, blood smear test abnormal	Very common

[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.

Hepatic dysfunction, characterised by jaundice, elevations in serum bilirubin, transaminases, and alkaline phosphatases, have occurred in patients receiving cytarabine alone or with other antineoplastic agents, but a causal relationship has not been definitely established.

As a consequence of extensive purine catabolism accompanying rapid cellular destruction, hyperuricaemia may occur in patients on cytarabine therapy; serum uric acid levels should be monitored. Hyperuricaemia may be minimised by adequate hydration, alkalinisation of the urine, and/or administration of allopurinol.

Adverse Effects During Experimental Dose Therapy

Although doses exceeding recommended dosage schedules have been used clinically and have been tolerated, severe and at time fatal adverse effects have been associated with high-dose cytarabine regimens (2.0 g - 3.0 g/m^2 given every 12 hours for 12 doses). These include the following adverse effects:

Table 2: Adverse Effects Table (Experimental Dose Therapy) (see Section 4.4 Special warnings and precautions for use)	
Infections and Infestations	
Sepsis, liver abscess	Frequency not known
Psychiatric Disorders	
Personality change[a]	Frequency not known
Nervous System Disorders	
Cerebral disorder, cerebellar disorder, somnolence	Very common
Coma, convulsion, peripheral motor neuropathy, peripheral sensory neuropathy	Frequency not known
Eye Disorders	
Haemorrhagic conjunctivitis, corneal disorder	Very common
Cardiac Disorders	
Cardiomyopathy[b], sinus bradycardia	Frequency not known
Respiratory, Thoracic and Mediastinal Disorders	
Acute respiratory distress syndrome, pulmonary oedema	Very common
Gastrointestinal Disorders	
Necrotising colitis	Common
Bowel necrosis, severe gastrointestinal ulcer, pneumatosis intestinalis, peritonitis	Frequency not known
Hepatobiliary Disorders	
Liver injury, hyperbilirubinaemia	Frequency not known
Skin and Subcutaneous Tissue Disorders	

Table 2: Adverse Effects Table (Experimental Dose Therapy) (see Section 4.4 Special warnings and precautions for use)	
Skin rash leading to desquamation, alopecia	Common

[a] Personality change was reported in association with cerebral and cerebellar dysfunction.
[b] With subsequent death.

Two patients with adult non-lymphocytic leukaemia developed peripheral motor and sensory neuropathies after consolidation with high dose cytarabine, daunorubicin and asparaginase.

Other Adverse Reactions

Experimental Dose Schedule

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary oedema and radiographically pronounced cardiomegaly has been reported following experimental high dose therapy of cytarabine for 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

Although systemic toxicity infrequently occurs with intrathecal administration of cytarabine, the haematologic status of the patient must be carefully monitored. Modification of the anti-leukaemic therapy may be required. The most frequently encountered adverse effects of intrathecal cytarabine are nausea, vomiting, transient headaches and fever, but these reactions are mild and self-limiting. Paraplegia has been reported.

Neurotoxicity following intrathecal cytarabine has been associated with preservative-containing diluents and many clinicians recommend the use of preservative-free diluents instead.

Blindness occurred in 2 patients with ALL during remission, who had received systemic combination chemotherapy, prophylactic CNS radiation as well as intrathecal cytarabine. Necrotising leukoencephalopathy with or without convulsions has been reported to have occurred in 5 children who had received triple intrathecal therapy consisting of cytarabine, methotrexate and hydrocortisone, and CNS irradiation. 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 at www.tga.gov.au/safety/reporting-problems.

4.9 Overdose

There is no antidote for cytarabine overdosage. Doses of 4.5 g/m^2 IV infusion over 1 hour every 12 hours for 12 doses have caused an unacceptable increase in irreversible CNS toxicity and even death. Severe bone marrow depression, gastrointestinal toxicity (ulceration and bleeding of the gastrointestinal tract), vomiting, nausea, diarrhoea, severe skin rash, CNS toxicity (including cerebral and cerebellar dysfunction), cardiac disorders, pulmonary and corneal toxicity, fever, myalgia, bone pain, chest pain and conjunctivitis are among the signs and symptoms expected. Treatment with cytarabine should be ceased and supportive measures instituted.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

The exact mechanism(s) of action of cytarabine is not fully understood, but cytarabine triphosphate appears to inhibit DNA synthesis by the inhibition of DNA polymerase. Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture. Cytarabine's actions are cell-cycle specific, 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. Deoxycytidine prevents or delays (but does not reverse) the cytotoxic activity.

Cytarabine is also immunosuppressant and has demonstrated antiviral activity *in vitro*. However, efficacy against *herpes zoster* or smallpox could not be demonstrated in controlled clinical trials.

Cytarabine is a synthetic pyrimidine nucleoside which is converted intracellularly to the nucleotide, 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.

5.2 Pharmacokinetic Properties

Absorption

Cytarabine is not effective when administered orally, less than 20% of a dose of cytarabine is absorbed from the gastrointestinal tract. 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

It is rapidly and widely distributed into tissues including liver, plasma and peripheral granulocytes. Cytarabine crosses the blood-brain barrier to a limited extent and also apparently crosses the placenta. 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

After rapid IV injection, plasma concentrations of cytarabine appear to decline in a biphasic manner with an initial distribution half-life of about 10 minutes, followed by an elimination half-life of about 1-3 hours.

Cytarabine is rapidly metabolised, mainly in the liver, to the inactive metabolite 1-β-D-arabinofuranosyluracil. 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 is excreted in the urine within 24 hours; approximately 90% as the metabolite and 10% as unchanged cytarabine.

5.3 Preclinical Safety Data

Genotoxicity

Extensive chromosomal damage, including chromatoid breaks, have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Hydrochloric acid

Sodium hydroxide

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special Precautions for Storage

Store at 15°C to 25°C. Protect from light.

If a precipitate has formed as a result of exposure to low temperatures, redissolve by warming up to 55°C for no longer than 30 minutes and shake until the precipitate has dissolved. Allow to cool prior to use.

6.5 Nature and Contents of Container

Strength and Container	Number of vials per pack
1 g per 10 mL in Type 1 clear glass vial	1
2 g per 20 mL in Type 1 clear glass vial	1

6.6 Special Precautions for Disposal

Spills and Disposal

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.

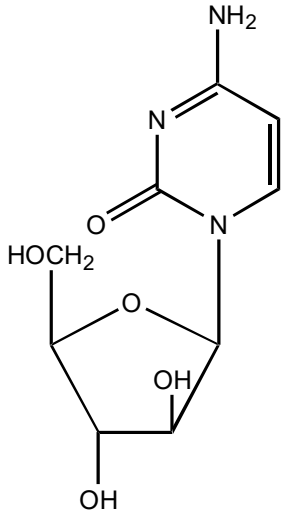
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical Properties

Cytarabine is a synthetic nucleoside which differs from the normal nucleosides cytidine and deoxycytidine in that the sugar moiety is arabinose rather than ribose or deoxyribose. It is a white or almost white, crystalline powder, freely soluble in water, very slightly soluble in alcohol and in methylene chloride.

Chemical structure

The structural formula of cytarabine is shown below:



CAS number

147-94-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number : 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

16 September 1992

10. DATE OF REVISION

01 April 2026

™ = Trademark

® = Registered trademark

Summary Table of Changes

Section changed	Summary of new information
Throughout	Minor editorial changes
4.2 & 6.6	Relocation of contents related to "Spills and Disposal" to section 6.6 and reference to new location added
4.8	Addition of "toxic erythema of chemotherapy" as cluster ADR and relocation of "palmar-plantar erythrodysaesthesia syndrome" to footnote. TGA reporting website corrected.
5.1 & 5.2	Relocation of contents related to "Immunosuppressive Action" from section 5.2 to section 5.1
8	Revised sponsor website