NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Cytarabine Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Cytarabine Injection 100 mg/mL is a solution of Cytarabine BP in Water for Injections.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

DBL Cytarabine Injection is a clear colourless sterile solution.

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.

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

4.2 Dose and 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.

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

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 milligrams/m^2/day, continuous IV infusion (days 1 to 7)
Daunorubicin:	45 milligrams/m^2/day, IV push (days 1 to 3)

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

Cytarabine, Thioguanine, Daunorubicin

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

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

Cytarabine, Doxorubicin

Cytarabine: 100 milligrams/m^2/day, continuous IV infusion (days 1 to 10)

Doxorubicin: 30 milligrams/m^2/day, IV infusion over 30 minutes (days 1 to 3)

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

Cytarabine, Doxorubicin, Vincristine, Prednisolone

Cytarabine: 100 milligrams/m^2/day, continuous IV infusion (days 1 to 7)

Doxorubicin: 30 milligrams/m^2/day, IV infusion (days 1 to 3)

Vincristine: 1.5 milligrams/m^2/day, IV infusion (days 1, 5)

Prednisolone: 40 milligrams/m^2/day, IV infusion every 12 hours (days 1 to 5)

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

Cytarabine, Daunorubicin, Thioguanine, Prednisone, Vincristine

Cytarabine: 100 milligrams/m^2/day, IV every 12 hours (days 1 to 7)

Daunorubicin: 70 milligrams/m^2/day, IV infusion (days 1 to 3)

Thioguanine: 100 milligrams/m^2 orally every 12 hours (days 1 to 7)

Prednisone: 40 milligrams/m^2/day, orally (days 1 to 7)

Vincristine: 1 milligram/m^2/day, IV infusion (days 1,7)

Additional courses (complete or modified) as required at 2 to 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

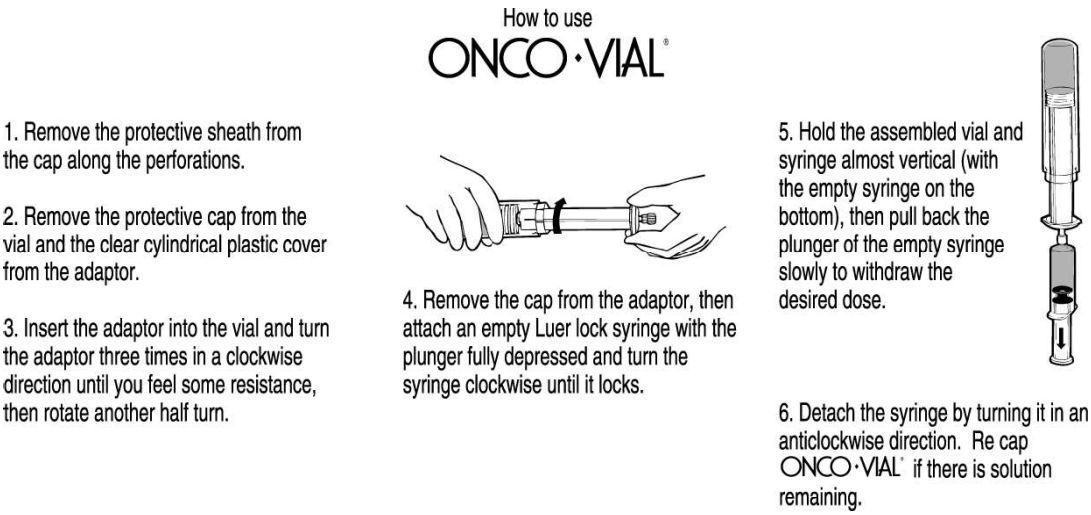
cerebrospinal fluid findings were normal, followed by one additional treatment. The dosage schedule is usually governed by the type and severity of central nervous system manifestations and the response to previous therapy (see section 4.8 Undesirable Effects).

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.

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

Directions for use of ONCO•VIAL™



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

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.

4.3 Contraindications

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

Anaemia, leukopenia and thrombocytopenia of non-malignant etiology (e.g. bone marrow aplasia), unless the benefits outweigh the risk.

Degenerative and toxic encephalopathies, especially after the use of methotrexate or treatment with ionising radiation.

During pregnancy, cytarabine should only be administered on strict indication, where the benefits of the drug to the mother should be weighed against possible hazards to the fetus.

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 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 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). Therapy should be suspended or modified when drug-induced bone marrow depression results in a platelet count of less than 50,000 or a polymorphonuclear count of under 1000 per 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. Therapy may be restarted when the bone marrow appears to be recovering on successive bone marrow studies. Therapy should not wait until the normal blood values are obtained to be re-initiated. If treatment is not resumed before blood values return to normal, the disease can get out of 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 checks of bone marrow, liver and kidney functions should be performed in patients receiving cytarabine, the drug should be used with caution in patients with impaired hepatic function.

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 hyperuricaemia secondary to rapid lysis of neoplastic cells; serum uric acid concentrations should be monitored. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacological measures as may be necessary to control this problem. Hyperuricaemia may be minimised by adequate hydration, alkalinisation of the urine, and/or administration of allopurinol.

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.

Concurrent granulocyte-transfusion should be avoided as severe respiratory insufficiency has been reported.

Experimental Doses

Severe and at times fatal central nervous system (CNS), gastrointestinal (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; cerebral and cerebellar dysfunction, usually reversible; somnolence; convulsion; severe gastrointestinal ulceration, including pneumatosis cystoides intestinallis, leading to peritonitis; sepsis and liver abscess, pulmonary oedema, liver damage with increased hyperbilirubinaemia; bowel necrosis; and necrotising colitis.

Corneal and conjunctival toxicities including reversible corneal lesion and haemorrhagic conjunctivitis have been reported. This may be prevented or diminished by prophylaxis with a local corticosteroid eye drop.

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

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.

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.

Hepatic and/or Renal Effects

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.

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.

Use in the Elderly

Although studies with cytarabine have not been performed in the geriatric population, geriatric-specific problems that would limit the usefulness of this medication in the elderly are not

expected. Elderly patients are, however, more likely to have age-related renal function impairment, which may require reduction of dosage in patients receiving cytarabine.

Paediatric population

Appropriate studies with cytarabine have not been performed in the paediatric population. However, paediatric-specific problems that would limit the usefulness of this medication in children are not expected.

4.5 Interaction with other medicines and other forms of interaction

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

Use with care following prior treatment with L-asparaginase (see section 4.4 Special Warnings and Precautions for Use):

- **Allopurinol, Colchicine, Probenecid or Sulphinpyrazone**: Cytarabine may raise the concentration of blood uric acid. Dosage adjustment of anti-gout agents may be necessary to control hyperuricaemia and gout. Allopurinol may be preferred to prevent or reverse cytarabine-induced hyperuricaemia because of risk of uric acid nephropathy with uricosuric antigout agents.

- **Blood Dyscrasia Causing Medications**: Leukopenic and/or thrombocytopenic effects of cytarabine may be increased with concurrent or recent therapy if these medications cause the same effects, dosage adjustment of cytarabine, if necessary, should be based on blood counts.

- **Bone Marrow Depressants or Radiation Therapy**: Additive bone marrow depression may occur; dosage reduction may be required when two or more bone marrow depressants, including radiation, are used concurrently or consecutively.

- **Cyclophosphamide**: Concurrent use with high-dose cytarabine therapy for bone marrow transplant preparation has been reported to result in an increase in cardiomyopathy with subsequent death.

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

- **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 decrease the intracellular activation of cytarabine. These factors should be considered when using the medicines concurrently.

  There is evidence of pharmacodynamics interaction between methotrexate and cytarabine leading to encephalopathy.

- **Digoxin:** GI absorption of oral digoxin tablets may be substantially reduced in patients receiving combination chemotherapy regimens (including regimens containing cytarabine), possibly as a result of temporary damage to intestinal mucosa caused by the cytotoxic agents. 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.

- **Immunosuppressive agents:** Due to the immunosuppressive action of cytarabine, 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 time fatal.

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.

Fertility

Fertility studies to assess the reproductive toxicity of cytarabine have not been conducted. Gonadal suppression, resulting in amenorrhea or azoospermia, may occur in patients taking cytarabine therapy, especially in combination with alkylating agents. In general, these effects appear to be related to dose and length of therapy and may be irreversible. Given that cytarabine has a mutagenic potential which could induce chromosomal damage in the human spermatozoa, males undergoing cytarabine treatment and their partner should be advised to use a reliable contraceptive method.

Pregnancy

Cytarabine is suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. It may also have adverse pharmacological effects. Cytarabine has been shown to be teratogenic in some animal species and should not be used during pregnancy, especially during the first trimester, nor in women likely to become pregnant.

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 in all three trimesters of pregnancy, follow-up of such infants would be advisable.

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, because of the risks to the infant (see sections 4.8 Undesirable Effects and 5.3 Preclinical Safety Data).

4.7 Effects on ability to drive and use machines

DBL Cytarabine for Injection has no influence on the ability to drive and use machines, nevertheless it is likely to produce severe adverse effects, which may impair the patient's ability to concentrate and react and therefore constitute a risk in the ability to drive and use machines.

4.8 Undesirable effects

Haematological

The major adverse effect of cytarabine is haematologic toxicity. 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.

Especially in treatment with high doses of cytarabine, more severe reactions may appear in addition to common symptoms. Intestinal perforation or necrosis with ileus and peritonitis has been reported. Pancreatitis has also been observed after high-dose therapy.

Infectious Complications

Viral, bacterial, fungal, parasitic, or saprophytic infection 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. These infections may be mild, but can be severe and at times fatal.

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

Cytarabine (Ara-C) Syndrome

A cytarabine syndrome (immunoallergic effect) characterised by fever, myalgia, bone pain, malaise, maculopapular rash, conjunctivitis, and occasionally chest pain, has been reported. A "flu-like" syndrome has been reported, which may be treated with corticosteroid therapy if severe. Anaphylactoid reactions have occurred. It normally occurs at 6 to 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.

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

Summary of Safety Profile (see section 4.4 Special Warnings and Precautions for Use)

Blood and lymphatic system disorders

Haematological toxicity has been seen as profound pancytopenia which may last 15-25 days along with more severe bone marrow aplasia than that observed at conventional doses.

Eye disorders

Reversible corneal lesion and haemorrhagic conjunctivitis have been reported. These can be prevented or decreased by prophylactic use of corticosteroid eye drops.

Hepatobiliary disorders

Liver abscesses, hepatomegaly and Budd-Chiari-syndrome (hepatic venous thrombosis) have been observed after high-dose therapy.

Respiratory, thoracic and mediastinal disorders

Clinical signs as present in pulmonary oedema/ARDS may develop, particularly in high-dose therapy. The reaction is probably caused by an alveolar capillary injury. It is difficult to make an assessment of frequencies (stated as 10-26% in different publications), since the patients usually have been in relapse where other factors may contribute to this reaction.

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% to <10%), Uncommon (≥0.1% to <1%), Rare (≥0.01% to <0.1%), Very rare (<0.01%) and Frequency not known (cannot be estimated from available data).

Adverse Effects Table

Infections and Infestations	
Very common	Sepsis (immunosuppression), pneumonia, infection[a]
Uncommon	Injection site cellulitis
Blood and Lymphatic System Disorders	
Very common	Anaemia, megaloblastosis, leukopenia, thrombocytopenia, bone marrow failure, reticulocyte count decreased
Immune System Disorders	
Uncommon	Anaphylactic reaction[b], allergic oedema
Metabolism and Nutrition Disorders	
Common	Anorexia, hyperuricaemia
Nervous System Disorders	
Common	At high doses cerebellar or cerebral influence with deterioration of the level of consciousness, dysarthria, nystagmus
Uncommon	Neurotoxicity, neuritis, dizziness, headache, peripheral neuropathy, paraplegia at intrathecal administration
Frequency not known	Neurotoxicity rash
Eye Disorders	
Common	Reversible haemorrhagic conjunctivitis (photophobia, burning, visual disturbance, increased lacrimation), keratitis
Uncommon	Conjunctivitis[c]
Cardiac Disorders	

Very rare	Arrhythmia, cardiomyopathy
Frequency not known	Pericarditis, sinus bradycardia
Vascular Disorders	
Common	Bleeding (all sites), thrombophlebitis
Respiratory, Thoracic and Mediastinal Disorders	
Uncommon	Pneumonia, dyspnoea, 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, pneumatosis cytoides intestinalis, necrotising colitis, peritonitis
Frequency not known	Gastrointestinal haemorrhage, pancreatitis, oral inflammation
Hepatobiliary Disorders	
Very common	Hepatic function abnormal, reversible effects on the liver with increased enzyme levels
Uncommon	Jaundice
Skin and Subcutaneous Tissue Disorders	
Very common	Alopecia, rash
Common	Skin ulceration, erythema, bullous dermatitis, urticaria, vasculitis, pruritus, burning pain of palms and soles
Uncommon	Toxic erythema of chemotherapy[e], urticaria, pruritus, ephelides
Very rare	Neutrophilic eccrine hidradenitis
Frequency not known	Skin bleeding
Musculoskeletal, Connective Tissue and Bone Disorders	
Very common	Cytarabine syndrome
Uncommon	Myalgia, joint pain
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]
Reproductive system and breast disorders	
Frequency not known	Amenorrheoa and azoospermia
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.

Adverse Effects Table (Experimental Dose Therapy) (see section 4.4 Special Warnings and Precautions for Use)

Infections and Infestations	
Frequency not known	Sepsis, liver abscess
Blood and lymphatic system disorders	
Frequency not known	Pancytopenia – may last 15-25 days with more severe bone marrow aplasia
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, reversible corneal lesion
Cardiac Disorders	
Frequency not known	Cardiomyopathy[b], sinus bradycardia
Respiratory, Thoracic and Mediastinal Disorders	
Very common	Acute respiratory distress syndrome, pulmonary oedema
Reproductive system and breast disorders	
Frequency not known	Amenorrhoea and azoospermia
Gastrointestinal Disorders	
Common	Necrotising colitis
Frequency not known	Bowel necrosis, gastrointestinal ulcer, pneumatosis intestinalis, peritonitis, pancreatitis
Hepatobiliary Disorders	
Frequency not known	Liver injury, hepatomegaly, Budd-Chiari-syndrome (hepatic venous syndrome), 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

Following cytarabine therapy, cardiomyopathy and rhabdomyolysis have been reported.

The gastrointestinal undesirable effects are reduced if cytarabine is administered as infusion. Local glucocorticoids are recommended as prophylaxis of haemorrhagic conjunctivitis.

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

Although systemic toxicity infrequently occurs with intrathecal administration of cytarabine, the haematologic status of the patient must be carefully monitored. Modification of the antileukaemic therapy may be required. The most frequently reported adverse reactions after intrathecal administration were nausea, vomiting and fever; 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.

Necrotising leukoencephalopathy with or without convulsions has been reported in 5 children who had received triple intrathecal therapy consisting of cytarabine, methotrexate and hydrocortisone, and central nervous system irradiation. Isolated neurotoxicity has been reported.

Blindness occurred in two patients with ALL during remission whose treatment 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

There is no antidote for cytarabine overdosage. Cessation of therapy followed by management of ensuing bone marrow depression including whole blood or platelet transfusion and antibiotics as required.

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.

Cytarabine may be removed by haemodialysis.

In bone marrow depression, transfusions of blood products may be required and active measures may be necessary to combat infection.

Hyperuricaemia is avoided by the addition of allopurinol to treatment schedules and measures such as alkalinisation of the urine and hydration may also be adopted.

Techniques attempting to prevent the occurrence of alopecia have met with varying success. Scalp tourniquets and ice packs have been used to minimise concentrations of antineoplastic agents in the scalp after intravenous injection. Such methods, however, may allow the development of a cancer-cell sanctuary and should not be used in patients with leukaemia or other conditions with circulating malignant cells.

The treatment of extravasation is controversial. Warm moist soaks or ice packs have been applied and a corticosteroid may sometimes be instilled into the affected area.

Antiemetic therapy should be given in an attempt to prevent or control nausea and vomiting.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Cytarabine is an antineoplastic agent. Cytarabine is a synthetic pyrimidine nucleoside, which is converted intracellularly to the nucleotide, cytarabine triphosphate. The exact mechanism of action of cytarabine is not fully understood, but cytarabine triphosphate appears to inhibit DNA synthesis by the inhibition of DNA polymerase. 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's actions are cell-cycle specific as it has no effect on non-proliferating cells, or on proliferating cells unless in the S or DNA synthesis phase. 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 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.

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.

5.2 Pharmacokinetic properties

Absorption

Cytarabine is not effective when administered orally, less than 20% of a dose 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

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 breast 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.

Biotransformation

Metabolism occurs also in the kidneys, gastrointestinal mucosa, granulocytes and other tissues. Cytarabine is rapidly metabolised, mainly in the liver, to the inactive metabolite 1-β-D-arabinofuranosyluracil.

Elimination

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 a secondary elimination half-life of about 1-3 hours.

About 70 to 80% of a dose is excreted in the urine of a dose administered by any route within 24 hours; approximately 90% as the metabolite and 10% as unchanged cytarabine.

5.3 Preclinical safety data

Genotoxicity

Cytarabine may cause chromosomal damage, including chromatoid breaks, in humans. Malignant transformation of rodent cells in culture has been reported.

Carcinogenicity

Secondary malignancies are potential delayed effects of many antineoplastic agents, although it is not clear whether the effect is related to their mutagenic or immunosuppressive action. The effect of dose and duration of therapy is also unknown, although risk seems to increase with long-term use.

Antimetabolites have been shown to be carcinogenic in animals and may be associated with an increased risk of development of secondary carcinomas in humans.

Reproductive and developmental toxicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid

Sodium hydroxide

Water for injection

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

18 months.

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

DBL Cytarabine Injection is presented in vials containing cytarabine as a sterile solution:

Strength and Container	**Pack Size**
100 mg per 1 mL in Type 1 clear glass vial	5 vials per pack
500 mg per 5 mL in Type 1 clear glass vial	5 vials per pack
1 g per 10 mL in Type 1 clear glass vial	1 vial per pack
2 g per 20 mL in Type 1 clear glass vial	1 vial per pack

Not all presentations may be marketed.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand
Toll Free Number: 0800 736 363
www.pfizermedicalinformation.co.nz

9. DATE OF FIRST APPROVAL

25 June 1992

10. DATE OF REVISION OF THE TEXT

12 February 2026

™ = Trademark

Summary table of changes

Section changed	Summary of new information
Throughout	Editorial changes
4.8	Addition of "toxic erythema of chemotherapy" as cluster ADR and relocation of "palmar-plantar erythrodysaesthesia syndrome" to footnote; Addition of urticaria & pruritus to align with Innovator. Removal of duplicate ADRs (liver abscesses, dizziness); removal of incorrect ADR (lentigo) - correct ADR is ephelides – to align with Innovator. AE reporting website updated
5.1 & 5.2	Relocated text regarding Immunosuppressive Action from 5.2 to 5.1
8	Addition of sponsor website