Cytarabine Injection

100 mg/mL
(100 mg/mL, 1g /10 mL, 2g /20 mL)

Hospira Standard
Sterile

THERAPEUTIC CLASSIFICATION
Antileukemic Agent
Pr Cytarabine Injection

100 mg/mL
(100 mg/mL, 1g/10 mL, 2g/20 mL)

Hospira Standard

Antileukemic Agent

PART I: HEALTH PROFESSIONAL INFORMATION

CAUTION: CYTARABINE INJECTION (CYTARABINE) SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER THERAPY DRUGS (SEE WARNINGS AND PRECAUTIONS). HEMATOLOGIC, RENAL, AND HEPATIC EVALUATIONS MUST BE DONE AT REGULAR INTERVALS.

ACTION AND CLINICAL PHARMACOLOGY

Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate, an effective inhibitor of DNA polymerase; it is inactivated by pyrimidine nucleoside deaminase which converts it to the non-toxic uracil derivative. It appears that the balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine.

Cytarabine is rapidly metabolized and is not effective orally; less than 20% of the orally administered dose is absorbed from the gastrointestinal tract.

Following rapid intravenous injection of cytarabine, the disappearance from plasma is biphasic. There is an initial distributive phase with a half-life of about 10 minutes, followed by a second elimination phase with a half-life of about 1 to 3 hours. After the distributive phase, over 80% of plasma radioactivity can be accounted for by the inactive metabolite 1-β-D-arabinofuranosyluracil (ara-U). Within 24 hours about 80% of the administered radioactivity can be recovered in the urine, approximately 90% of which is excreted as ara-U.

After subcutaneous or intramuscular administration of cytarabine, peak plasma levels of radioactivity are achieved about 20 to 60 minutes after injection and are considerably lower than those after intravenous administration.

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% 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.

INDICATIONS AND CLINICAL USE

Cytarabine Injection (cytarabine) is indicated primarily for induction and maintenance of remission in acute leukemia in both adults and children.

It has been found useful in the treatment of acute myelocytic leukemia, chronic myelocytic leukemia (blast phase), acute lymphocytic leukemia and erythroleukemia. Cytarabine may be used alone or in combination with other antineoplastic agents; the best results are obtained with combination therapy.

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

Cytarabine has been used intrathecally in newly diagnosed children with acute lymphocytic leukemia as well as in the treatment of meningeal leukemia.

Cytarabine, in high dose 2 to 3 g/m² as an intravenous infusion over 1 to 3 hours given every 12 hours for 2 to 6 days with or without additional cancer chemotherapeutic agents, has been shown to be effective in the treatment of poor-risk leukemia, refractory leukemia, and relapsed acute leukemia.

Remissions induced by cytarabine not followed by maintenance treatment have been brief.

CONTRAINDICATIONS

Cytarabine Injection (cytarabine) is contraindicated in those patients who are hypersensitive to the drug.

WARNINGS AND PRECAUTIONS

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

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

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.

Benzyl alcohol has been reported to be associated with a fatal “Gasping Syndrome” in pediatric patients. As premature and low weight infants may be at increased risk of developing this toxicity, they should not be given cytarabine reconstituted with a diluent containing benzyl alcohol (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

If high dose therapy is used, do not use a diluent containing benzyl alcohol.

Do not use a diluent containing benzyl alcohol if using intrathecally.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
Extensive chromosomal damage, including chromatoid breaks, has been produced by cytarabine and malignant transformation of rodent cells in culture has been reported. Cytarabine is embryotoxic and teratogenic and produced peri- and postnatal toxicity in various species. Sperm head abnormalities were observed following cytarabine treatment in mice (See TOXICOLOGY).

**Cardiovascular**
High-dose schedules: An increase in cardiomyopathy with subsequent death has been reported following experimental high-dose cytarabine and cyclophosphamide therapy when used for bone marrow transplant preparation. This may be schedule-dependent.

**Gastrointestinal**
Abdominal tenderness (peritonitis) and Typhlitis 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 nonoperative medical management.

High-dose schedule: Severe and at times fatal GI toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following high-dose (2 to 3 g/m²) schedules of cytarabine. These reactions include severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis, leading to peritonitis, bowel necrosis; and necrotizing colitis.

**Genitourinary**
Tumour Lysis Syndrome: Like other cytotoxic drugs, cytarabine may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacologic measurements as might be necessary to control this problem.
Hematologic Effects
Cytarabine is a potent bone marrow suppressant; the severity depends on the dose of the drug and schedule of administration. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression. Patients receiving this drug must be under close medical supervision and, during induction therapy, should have leukocyte and platelet counts performed daily. Bone marrow examinations should be performed frequently after blasts have disappeared from the peripheral blood. Facilities should be available for management of complications (possibly fatal) of bone marrow suppression (infection resulting from granulocytopenia and other impaired body defenses, and hemorrhage secondary to thrombocytopenia).

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

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

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

High-dose schedules: Other reactions have been reported following high-dose (2 to 3 g/m²) schedules of cytarabine and include sepsis and liver abscess, and liver damage with increased hyperbilirubinemia.

Hypersensitivity Reactions
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.

Immune
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.

Neurologic
High-dose schedules: Severe and at times fatal CNS toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following high-dose (2 to 3 g/m²) schedules of cytarabine. These reactions include cerebral and cerebellar dysfunction including personality changes, somnolence, convulsion and coma, usually reversible.
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.

Cases of severe neurological adverse reactions that ranged from headache to paralysis, come and stroke-like episodes have been reported mostly in pediatric patients given intravenous cytarabine in combination with intrathecal methotrexate.

**Ophthalmologic**

High-dose schedules: The following reactions have been reported following high-dose (2 to 3 g/m²) schedules of cytarabine: reversible corneal toxicity and hemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with a local corticosteroid eye drop.

**Respiratory**

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

**Skin**

Palmar plantar erythrodysaesthesia: Palmar plantar erythrodysaesthesia (PPE) has occurred with cytarabine treatment in adults and children. Severe cytarabine associated PPE that resulted in treatment discontinuation has been reported.

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

**Special Populations**

**Pregnant Women**

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

Normal infants have been born to mothers exposed to cytarabine during pregnancy (alone or in combination with other drugs); some of these infants were premature or of low birth weight. Some of the normal infants were followed up at ages ranging from six weeks to seven years following exposure, and showed no abnormalities. One apparently normal infant died at 80 days of gastroenteritis.

Congenital abnormalities have been reported, particularly when the fetus has been exposed to systemic therapy with cytarabine during the first trimester. These include upper and lower distal limb defects, and extremity and ear deformities.
Reports of pancytopenia, leucopenia, anemia, thrombocytopenia, electrolyte abnormalities, transient oesinophilia, increased IgM levels and hyperpyrexia, sepsis and death have occurred during the neonatal period to infants exposed to cytarabine in utero. Some of these infants were also premature.

Therapeutic abortions have been done in pregnant women on cytarabine. Normal fetuses have been reported while other reported fetal effects included enlarged spleen and Trisomy C chromosome abnormality in the chorionic tissue.

Because of the potential for abnormalities with cytotoxic therapy, particularly during the first trimester, a patient who is or who becomes 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.

**Nursing Women**

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

**Pediatrics**

The safety of this drug for use in infants (under 1 year of age) is not established.

Gasping Syndrome: Cytarabine should not be given to premature and low birth weight infants when using a diluent that contains benzyl alcohol. The preservative benzyl alcohol has been associated with serious adverse events, including the “gasp syndrome”, and death in pediatric patients. Symptoms of gasping syndrome may include metabolic acidosis, seizure, bradycardia, gasping respiration and cardiovascular collapse. Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasing syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the hepatic capacity to detoxify the chemical. Premature and low birth weight infants may be more likely to develop toxicity. If cytarabine is used in high-dose or intrathecal therapy, do not use a diluent containing benzyl alcohol. The preservative-free 0.9% sodium chloride can be used for reconstitution.

See Also WARNING AND PRECAUTIONS: Neurologic.

**Monitoring and Laboratory Tests**

Patients receiving Cytarabine Injection (cytarabine) must be monitored closely. Frequent platelet and leukocyte counts and bone marrow examinations are mandatory. Consider suspending or modifying therapy when drug-induced marrow depression has resulted in a platelet count under 50 000 or a polymorphonuclear granulocyte count under 1000/mm³. 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 or 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.

**Interaction with Other Medicinal Products**

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

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

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

**Methotrexate:** Intravenous cytarabine given concomitantly with intrathecal methotrexate may increase the risk of severe neurological adverse reactions such as headache, paralysis, coma and stroke-like episodes.

**ADVERSE REACTIONS**

**Blood and Lymphatic System Disorders**

Because cytarabine is a bone marrow suppressant, anemia, leukopenia, thrombocytopenia, megaloblastosis, and reduced reticulocytes can be expected as a result of its administration. The severity of these reactions are dose- and schedule-dependent. Cellular changes in the morphology of bone marrows and peripheral smears can be expected.

Following 5-day constant infusions or acute injections of 50 mg/m² to 600 mg/m², 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 to 9. This is followed by a brief rise which peaks around the twelfth day. A second and deeper fall reaches nadir at days 15 to 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 to 15. Thereupon, a rapid rise to above baseline occurs in the next 10 days.

**Infections and Infestations**

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

**Musculoskeletal and Connective Tissue Disorders**

**The Cytarabine Syndrome**
A cytarabine syndrome has been described by Castleberry RP, Crist WM, Holbrook T, et al. It is
characterized by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash,
conjunctivitis and malaise. It usually occurs 6 to 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.

**Other Adverse Reactions**

**Conventional-Dose Therapy**
Nausea and vomiting are most frequent following rapid intravenous injection.

**Table 1: Adverse Reactions (with conventional-dose therapy)**: The reported adverse reactions are
listed below by MedDRA System Organ Class and by frequency. Frequencies are defined as: Very
common (>10%), Common (>1%, ≤10%), Uncommon (>0.1%, ≤1%), Rare (>0.01%, ≤0.1%), and
Frequency not known (cannot be estimated from available data).

<table>
<thead>
<tr>
<th>Blood and Lymphatic System Disorders:</th>
<th>Very common</th>
<th>Bone marrow failure, thrombocytopenia, anemia, anemia megaloblastic, leukopenia, reticulocyte count decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency not known</td>
<td>Bleeding (all sites)</td>
</tr>
<tr>
<td><strong>Cardiac Disorders:</strong></td>
<td>Frequency not known</td>
<td>Pericarditis</td>
</tr>
<tr>
<td><strong>Eye Disorders:</strong></td>
<td>Frequency not known</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders:</strong></td>
<td>Very common</td>
<td>Stomatitis, mouth ulceration, anal ulcer, anal inflammation, diarrhea, vomiting, nausea, abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Frequency not known</td>
<td>Bowel necrosis, pancreatitis, oesophageal ulcer, oesophagitis</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions:</strong></td>
<td>Very common</td>
<td>Pyrexia</td>
</tr>
<tr>
<td></td>
<td>Frequency not known</td>
<td>Chest pain, injection site reaction</td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders:</strong></td>
<td>Very common</td>
<td>Hepatic function abnormal</td>
</tr>
<tr>
<td></td>
<td>Frequency not known</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Infections and Infestations:</td>
<td>Very common</td>
<td>Sepsis, pneumonia, infection&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Frequency not known</td>
<td>Injection site cellulitis</td>
<td></td>
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</table>

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<thead>
<tr>
<th>Immune System Disorders:</th>
<th>Frequency not known</th>
<th>Anaphylactic reaction, allergic edema</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Investigations:</th>
<th>Very common</th>
<th>Biopsy bone marrow abnormal, blood smear test abnormal</th>
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</thead>
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<thead>
<tr>
<th>Metabolism and Nutrition Disorders:</th>
<th>Frequency not known</th>
<th>Decreased appetite</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal, Connective Tissue and Bone Disorders:</th>
<th>Very common</th>
<th>Cytarabine syndrome</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Nervous System Disorders:</th>
<th>Very common</th>
<th>Neurotoxicity, neuritis, dizziness, headache</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Renal and Urinary Disorders:</th>
<th>Frequency not known</th>
<th>Renal impairment, urinary retention</th>
</tr>
</thead>
</table>

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<thead>
<tr>
<th>Respiratory, Thoracic and Mediastinal Disorders:</th>
<th>Frequency not known</th>
<th>Dyspnea, oropharyngeal pain</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Skin and Subcutaneous Tissue Disorders:</th>
<th>Very common</th>
<th>Alopecia, rash</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Skin ulcer</td>
<td></td>
</tr>
<tr>
<td>Frequency not known</td>
<td>Palmar-plantar erythrodysaesthesia syndrome, urticaria, pruritus, freckling</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular Disorders:</th>
<th>Frequency not known</th>
<th>Thrombophlebitis</th>
</tr>
</thead>
</table>

<sup>a</sup> May occur with rash and may be hemorrhagic with high-dose therapy.
<sup>b</sup> Pain and inflammation at subcutaneous injection site.
<sup>c</sup> May be mild, but can be severe and at times fatal.

**High-Dose Therapy**

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine) have been reported following high-dose schedules (2.0 g to 3.0 g/m<sup>2</sup> given every 12 hours for 12 doses).

**Table 2: Adverse Reactions (with high-dose therapy):** The reported adverse reactions are listed below by MedDRA System Organ Class and by frequency. Frequencies are defined as: Very common (>10%), Common (>1%, ≤10%), Uncommon (>0.1%, ≤1%), Rare (>0.01%, ≤0.1%), and Frequency not known (cannot be estimated from available data).

<table>
<thead>
<tr>
<th>Cardiac Disorders:</th>
<th>Frequency not known</th>
<th>Cardiomyopathy&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Eye Disorders:</th>
<th>Very common</th>
<th>Corneal disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency not known</td>
<td>Hemorrhagic conjunctivitis&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
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</table>

| Gastrointestinal Disorders: | | |
|-----------------------------| | |

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<table>
<thead>
<tr>
<th>Frequency not known</th>
<th>Gastrointestinal necrosis, gastrointestinal ulcer, pneumatosis intestinalis, peritonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency not known</td>
<td>Liver injury, hyperbilirubinemia</td>
</tr>
<tr>
<td>Very common</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Frequency not known</td>
<td>Liver abscess</td>
</tr>
<tr>
<td>Very common</td>
<td>Cerebral disorder, cerebellar disorder, somnolence</td>
</tr>
<tr>
<td>Frequency not known</td>
<td>Coma, convulsion, peripheral motorneuropathy, peripheral sensory neuropathy</td>
</tr>
<tr>
<td>Frequency not known</td>
<td>Personality change c</td>
</tr>
<tr>
<td>Very common</td>
<td>Acute respiratory distress syndrome, pulmonary edema</td>
</tr>
<tr>
<td>Common</td>
<td>Skin exfoliation</td>
</tr>
</tbody>
</table>

a With subsequent death.
b May be prevented or diminished by prophylaxis with a local corticosteroid eyedrop.
c Personality change was reported in association with cerebral and cerebellar dysfunction.

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

Corneal toxicity consisting of ocular pain, tearing, foreign-body sensation, photophobia and blurred vision has been reported.

Severe skin rash leading to desquamation has rarely been reported. Complete alopecia is more commonly seen with high-dose therapy than with standard cytarabine treatment programs.

If high-dose therapy is used, do not use a diluent containing benzyl alcohol.

**Intermediate-Dose Therapy**
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/m²) with and without other chemotherapeutic agents (meta-AMSA, daunorubicin, VP-16).
Intrathecal Therapy
Cytarabine given intrathecally may cause systemic toxicity and careful monitoring of the hemopoietic system is indicated. Modification of other anti-leukemia therapy may be necessary. Major toxicity is rare. 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. When cytarabine is administered both intrathecally and intravenously within a few days, there is an increased risk of spinal cord toxicity; however, in serious life-threatening disease, concurrent use of intravenous and intrathecal cytarabine is left to the discretion of the treating physician.

Symptoms and Treatment of Overdose
There is no antidote for Cytarabine Injection (cytarabine) overdose.

Discontinuation of the drug and supportive therapy are of course indicated. Transfusions of platelets should be given if there is any sign of hemorrhage. Patients should be carefully observed for intercurrent infection and, if such appears, they should be rapidly and rigorously treated with appropriate antibiotic therapy.

Chronic overdose may cause serious bone marrow suppression. Daily hematological evaluation should be performed to prevent overdose. Nausea and vomiting, although a general side effect of the drug, may be an additional warning of overdose. Severe hemorrhage into the gastrointestinal tract may indicate overdose as may severe generalized infections.

Doses exceeding recommended dosage schedules have been used clinically and have been tolerated. The major toxicity with the use of \(3 \text{ g/m}^2\) intravenous infusion over 1 hour every 12 hours for 12 doses and \(3 \text{ g/m}^2\) continuous infusion for 4 days, other than reversible bone marrow suppression, has been reversible corneal, cerebral and cerebellar dysfunction. Doses of \(4.5 \text{ g/m}^2\) intravenous infusion over 1 hour every 12 hours for 12 doses has caused an unacceptable increase in irreversible CNS toxicity and death.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Dosage and Administration

Caution
The following precautionary measures are recommended in proceeding with the preparation and handling of cytotoxic agents such as cytarabine.
1. The procedure should be carried out in a vertical laminar flow hood (Biological Safety Cabinet - Class II).

2. Personnel should wear: PVC gloves, safety glasses, disposable gowns and masks.

3. All needles, syringes, vials, and other materials which have come in contact with cytarabine should be segregated and destroyed by incineration (sealed containers may explode). If incineration is not available, neutralization should be carried out using 5% sodium hypochlorite, or 5% sodium thiosulfate.

4. Personnel regularly involved in the preparation and handling of cytarabine should have biannual hematologic examinations.

Cytarabine is not active orally. The schedule and method of administration varies with the program of therapy to be used. Cytarabine may be given by intravenous infusion, injection/subcutaneously or intrathecally. When preparing cytarabine for intravenous high-dose therapy or intrathecal use, do not use diluents containing benzyl alcohol (see PHARMACEUTICAL INFORMATION). It is recommended that cytarabine be reconstituted with preservative-free 0.9% sodium for injection and used immediately.

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 to somewhat parallel fashion to these different modes of administration and no clear-cut clinical advantage has been demonstrated for either.

Clinical experience accumulated to date suggests that success with cytarabine is dependent more on adeptness in modifying day-to-day dosage to obtain maximum leukemic cell kill with tolerable toxicity than on the basic treatment schedule chosen at the outset of therapy. Toxicity necessitating dosage alteration almost always occurs.

Relatively constant plasma levels can be achieved by continuous intravenous infusion.

In many chemotherapeutic programs, cytarabine is used in combination with other cytotoxic drugs. The addition of these cytotoxic drugs has necessitated changes and dose alterations. The dosage schedules for combination therapy outlined below have been reported in the literature (see References).
**DOSAGE SCHEDULES**

**Acute Myelocytic Leukemia - Induction Remission: Adults**
Cytarabine 200 mg/m² daily by continuous infusion for 5 days (120 hours) - total dose 1000 mg/m². This course is repeated approximately every 2 weeks. Modifications must be made based on hematologic response.

**Acute Myelocytic Leukemia - Maintenance: Adults**
Maintenance programs are modifications of induction programs and, in general, use similar schedules of drug therapy as were used during induction. Most programs have greater time spacing between courses of therapy during remission maintenance.

**Acute Myelocytic Leukemia - Induction and Maintenance: Children**
Numerous studies have shown that childhood AML responds better than adult AML given similar regimens. Where the adult dosage is stated in terms of body weight or surface area, the children's dosage may be calculated on the same basis. When specified amounts of a drug are indicated for the adult dosage, these should be adjusted for children on the basis of such factors as age, body weight or body surface area.

**Acute Myelocytic Leukemia – Adults and Children**
The following tables outline the results of treatment with cytarabine alone and in combination with other chemotherapeutic agents, in the treatment of acute myelocytic leukemia in adults and children.

The treatment regimens outlined in the tables should not be compared for efficacy. These were independent studies with a number of variables involved, such as patient population, duration of disease, and previous treatment.

The responsiveness and course of childhood acute myelocytic leukemia (AML) appear to be different from that in adults. Numerous studies show response rates to be higher in children than in adults with similar treatment schedules. Experience indicates that at least with induction and initial drug responsiveness, childhood AML appears to be more similar to childhood acute lymphocytic leukemia (ALL) than to its adult variant.
<table>
<thead>
<tr>
<th>Drug Dosage Schedule*</th>
<th>No. of Patients Evaluated</th>
<th>Complete Remissions</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytarabine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-Dose Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Infusion)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg/m² 12 hrs/day</td>
<td>12</td>
<td>2 (17%)</td>
<td>Ellison (1968)</td>
</tr>
<tr>
<td>30 mg/m² 12 hrs/day</td>
<td>41</td>
<td>10 (24%)</td>
<td></td>
</tr>
<tr>
<td>10 mg/m² 24 hrs/day</td>
<td>9</td>
<td>2 (22%)</td>
<td></td>
</tr>
<tr>
<td>30 mg/m² 24 hrs/day</td>
<td>36</td>
<td>2 (6%)</td>
<td></td>
</tr>
<tr>
<td>(Infusion)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg/m² 24 hrs/5 days</td>
<td>36</td>
<td>9 (25%)</td>
<td>Bodey (1969)</td>
</tr>
<tr>
<td>10 mg/m² intravenous injection initially, then infusions of 30 mg/m² per 12 hrs or 60 mg/m²/day for 4 days</td>
<td>49</td>
<td>21 (43%)</td>
<td>Goodell (1970)</td>
</tr>
<tr>
<td>(Infusion Therapy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>800 mg/m²/ 2 days</td>
<td>53</td>
<td>12 (23%)</td>
<td>Southwest Oncology Group (1974)</td>
</tr>
<tr>
<td>1000 mg/m²/5 days</td>
<td>60</td>
<td>24 (40%)</td>
<td></td>
</tr>
<tr>
<td>100 mg/m²/day 1 hr infusion</td>
<td>49</td>
<td>7 (14%)</td>
<td>Carey (1975)</td>
</tr>
<tr>
<td>5 to 12.5 mg/kg/12 hrs infusion following intravenous synchronizing dose**</td>
<td>5</td>
<td>5 (100%)</td>
<td>Lampkin (1976)</td>
</tr>
<tr>
<td><strong>Combined Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cytarabine-doxorubicin</td>
<td>41</td>
<td>30 (73%)</td>
<td>Preisler (1979)</td>
</tr>
<tr>
<td>cytarabine-thioguanine daunorubicin</td>
<td>28</td>
<td>22 (79%)</td>
<td>Gale (1977)</td>
</tr>
<tr>
<td>cytarabine-doxorubicin vincristine prednisolone</td>
<td>35</td>
<td>23 (66%)</td>
<td>Weinstein (1980)</td>
</tr>
<tr>
<td>cytarabine-daunorubicin thioguanine prednisone vincristine</td>
<td>139</td>
<td>84 (60%)</td>
<td>Glucksberg (1981)</td>
</tr>
<tr>
<td>cytarabine-daunorubicin</td>
<td>21</td>
<td>14 (67%)</td>
<td>Cassileth (1977)</td>
</tr>
<tr>
<td><strong>High-Dose Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>7</td>
<td>6 (86%)</td>
<td>Lister (1983)</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>21</td>
<td>12 (57%)</td>
<td>Herzig (1983)</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>11</td>
<td>8 (73%)</td>
<td>Preisler (1983)</td>
</tr>
<tr>
<td>cytarabine-doxorubicin</td>
<td>14</td>
<td>7 (50%)</td>
<td>Willemze (1982)</td>
</tr>
<tr>
<td>cytarabine-asparaginase</td>
<td>13</td>
<td>9 (69%)</td>
<td>Capizzi (1983)</td>
</tr>
</tbody>
</table>

* Unless otherwise stated, all doses given until drug effect - modifications then based on hematologic reasons. See references.

** Highly experimental - requires ability to study mitotic indices.
Table 4: Acute Myelocytic Leukemia- Remission Induction: Children (21 and under)

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>No. of Patients Evaluated</th>
<th>Complete Remissions</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytarabine (5-12.5 mg/kg following i.v. synchronizing dose**)</td>
<td>16</td>
<td>12 (75%)</td>
<td>Lampkin (1976)</td>
</tr>
<tr>
<td>Cytarabine, vincristine, doxorubicin, prednisolone</td>
<td>48</td>
<td>35 (73%)</td>
<td>Weinstein (1980)</td>
</tr>
<tr>
<td>Cytarabine, thioguanine, doxorubicin</td>
<td>11</td>
<td>8 (72%)</td>
<td>Hagbin (1975)</td>
</tr>
<tr>
<td>Cytarabine, thioguanine</td>
<td>47</td>
<td>20 (43%)</td>
<td>Pizzo (1976)</td>
</tr>
<tr>
<td>Cytarabine, cyclophosphamide</td>
<td>12</td>
<td>7 (58%)</td>
<td>Pizzo (1976)</td>
</tr>
</tbody>
</table>

** Highly experimental - requires ability to study mitotic indices.

Acute Lymphocytic Leukemia

In general, dosage schedules are similar to those used in acute myelocytic leukemia with some modification. Cytarabine has been used in the treatment of acute lymphocytic leukemia in both adults and children. When cytarabine was used with other antineoplastic agents as part of a total therapy program, results were equal to or better than reported with such programs which did not include cytarabine. Used singly, or in combination with other agents, cytarabine has also been effective in treating patients who had relapsed on other therapy. Table 5 and Table 6 summarize the results obtained in previously treated patients. Since these are independent studies with such variables as patient population, duration of disease and previous treatment, results shown should not be used for comparing the efficacy of the outlined treatment programs.

Table 5: Acute Lymphocytic Leukemia- Remission Induction: Previously Treated Patients Adults and Children

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>No. of Patients Evaluated</th>
<th>Complete Remissions</th>
<th>Response</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytarabine 3 to 5 mg/kg/day (intravenous injection)</td>
<td>43</td>
<td>2 (5%)</td>
<td>15 (35%)</td>
<td>Howard (1968)</td>
</tr>
<tr>
<td>Cytarabine- asparaginase</td>
<td>9</td>
<td>8 (89%)</td>
<td>8 (89%)</td>
<td>McElwain (1969)</td>
</tr>
<tr>
<td>Cytarabine- cyclophosphamide</td>
<td>11</td>
<td>7 (64%)</td>
<td>9 (82%)</td>
<td>Bodey (1970)</td>
</tr>
<tr>
<td>Cytarabine- prednisone</td>
<td>83</td>
<td>---</td>
<td>(49%)</td>
<td>Nesbitt (1970)</td>
</tr>
<tr>
<td>Cytarabine- 150 to 200 mg/m²/ 5 days (infusion)</td>
<td>34</td>
<td>1 (3%)</td>
<td>4 (12%)</td>
<td>Wang (1970)</td>
</tr>
<tr>
<td>Cytarabine- L-asparaginase- prednisone- vincristine- doxorubicin</td>
<td>91</td>
<td>72 (79%)</td>
<td>---</td>
<td>Klemperer (1978)</td>
</tr>
<tr>
<td>Cytarabine- L-asparaginase- prednisone- vincristine- doxorubicin</td>
<td>55</td>
<td>42 (76%)</td>
<td>---</td>
<td>Klemperer (1978)</td>
</tr>
<tr>
<td>Cytarabine- asparaginase</td>
<td>22</td>
<td>13 (59%)</td>
<td>15 (68%)</td>
<td>Ortega (1972)</td>
</tr>
<tr>
<td>Cytarabine- thioguanine</td>
<td>19</td>
<td>9 (47%)</td>
<td>9 (47%)</td>
<td>Bryan (1974)</td>
</tr>
</tbody>
</table>
Table 6

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>No. of patients evaluated</th>
<th>Complete Remissions</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-Dose Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>8</td>
<td>3 (38%)</td>
<td>Rohatinar (1983)</td>
</tr>
<tr>
<td>Cytarabine- doxorubicin</td>
<td>3</td>
<td>2 (67%)</td>
<td>Willemze (1982)</td>
</tr>
<tr>
<td>Cytarabine- asparaginase</td>
<td>10</td>
<td>3 (30%)</td>
<td>Capizzi (1983)</td>
</tr>
</tbody>
</table>

Non-Hodgkin's Lymphoma in Children

Cytarabine has been used as part of a multi-drug program (LSA₂L₂) to treat non-Hodgkin's lymphoma in children. See Appendix A for complete dosage schedule.

High-Dose Chemotherapy

Before instituting a program of high-dose chemotherapy, the physician should be familiar with the literature, adverse reactions, precautions, contraindications, and warnings applicable to all the drugs involved in the program.

Cytarabine

- Cytarabine: 2 g/m² infused over 3 hours every 12 hours x 12 doses (Days 1 to 6).

Cytarabine

- Cytarabine: 3 g/m² infused over 1 hour every 12 hours x 12 doses (Days 1 to 6).

Cytarabine

- Cytarabine: 3 g/m² infused over 75 minutes every 12 hours x 12 doses (Days 1 to 6).

Cytarabine - doxorubicin

- Cytarabine: 3 g/m² infused over 2 hours every 12 hours x 12 doses (Days 1 to 6).
- Doxorubicin: 30 mg/m² intravenous on Days 6-7.

Cytarabine - asparaginase

- Cytarabine: 3 g/m² infused over 3 hours at 0 hours, 12 hours, 24 hours, and 36 hours. At 42 hours, 6000 units/m² of asparaginase intramuscular. (Days 1 to 2); repeat same schedule Days 8 to 9.

Combined Chemotherapy

Before instituting a program of combined chemotherapy, the physician should be familiar with the literature, adverse reactions, precautions, contraindications, and warnings applicable to all the drugs involved in the program.

Cytarabine, doxorubicin

- Cytarabine: 100 mg/m²/day, continuous intravenous infusion (Days 1 to 10).
- Doxorubicin: 30 mg/m²/day, intravenous infusion of 30 minutes (Days 1 to 3).
Additional (complete or modified) courses as necessary at 2 to 4 week intervals if leukemia is persistent.

**Cytarabine, thioguanine, daunorubicin**
- Cytarabine: 100 mg/m², intravenous infusion over 30 minutes every 12 hours (Days 1 to 7).
- Thioguanine: 100 mg/m², orally every 12 hours (Days 1 to 7).
- Daunorubicin: 60 mg/m²/day, intravenous infusion (Days 5 to 7).

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

**Cytarabine, doxorubicin, vincristine, prednisone**
- Cytarabine: 100 mg/m²/day, continuous intravenous infusion (Days 1 to 7).
- Doxorubicin: 30 mg/m²/day, intravenous infusion (Days 1 to 3).
- Vincristine: 1.5 mg/m²/day, intravenous infusion (Days 1, 5)
- Prednisolone: 40 mg/m²/day, intravenous infusion every 12 hours (Days 1 to 5).

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

**Cytarabine, daunorubicin, thioguanine, prednisone, vincristine**
- Cytarabine: 100 mg/m²/day, intravenous infusion (Days 1 to 10).
- Daunorubicin: 70 mg/m²/day, intravenous infusion (Days 1 to 3).
- Thioguanine: 100 mg/m², orally every 12 hours (Days 1 to 7).
- Prednisone: 40 mg/m²/day, orally (Days 1 to 7).
- Vincristine: 1 mg/m²/day, intravenous infusion (Days 1, 7).

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

**Cytarabine, daunorubicin**
- Cytarabine: 100 mg/m²/day, continuous intravenous infusion (Days 1 to 7).
- Daunorubicin: 45 mg/m²/day, intravenous push (Days 1 to 3).

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

**Meningeal Leukemia - Intrathecal Use**
Cytarabine has been used intrathecally in acute leukemia in doses ranging from 5 mg/m² to 75 mg/m² 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/m² 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 SOLU-CORTEFTM Sterile Powder and methotrexate, both as prophylaxis in newly diagnosed children with acute lymphocytic leukemia, as well as in the treatment of meningeal leukemia. Sullivan has reported that prophylactic triple therapy has prevented late CNS disease and given overall cure and survival rates similar to those seen in patients in whom CNS radiation and intrathecal methotrexate was used as initial CNS prophylaxis. The dose of cytarabine was 30 mg/m², Solu-Cortef 15 mg/m², and methotrexate 15 mg/m². The physician should be familiar with this report before initiation of the regimen.

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

Cytarabine given intrathecally may cause systemic toxicity and careful monitoring of the hemopoietic system is indicated. Modification of the anti-leukemia therapy may be necessary. Major toxicity is rare. 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 occurred in 5 children; these patients had also been treated with intrathecal methotrexate and 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.

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

If used intrathecally, do not use a diluent containing benzyl alcohol. Reconstitute with preservative-free saline and use immediately.

**Dosage Modification**

The dosage of Cytarabine Injection (cytarabine) must be modified or suspended when signs of serious hematologic depression appear. In general, consider discontinuing the drug if the patient has less than 50 000 platelets or 1000 polymorphonuclear granulocytes/mm³ in his peripheral blood. These guidelines may be modified depending on signs of toxicity in other systems and on the rapidity of fall in formed blood elements. Restart the drug when there are signs of marrow recovery and the above platelet and granulocyte levels have been attained. Withholding therapy until the patient's blood values are normal may result in escape of the patient's disease from control by the drug.
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Chemical Structure:

Proper Name: Cytarabine

Chemical Name: 4-amino-1-β-D-arabinofuranosyl-2(1H)-pyrimidinone

Molecular Formula: C_9H_{13}N_3O_5

Molecular Weight: 243.2 g/mol

Description: Cytarabine occurs as an odourless, white to off-white crystalline powder. It is soluble in 1 in 10 of water and 1 in 1000 of alcohol and chloroform. A 2% solution in water has a pH of 4 to 6.

Composition: Cytarabine Injection is a sterile, preservative-free solution of cytarabine 100 mg/mL in water for injection. May contain sodium hydroxide or hydrochloric acid as pH adjusters.

Preparation for Use

Subcutaneous and Intravenous Injection
Cytarabine Injection is suitable for subcutaneous or intravenous injection.

Intravenous Infusion
Cytarabine Injection may be further diluted to 0.1 mg/mL for intravenous infusion with any of the solutions listed below.
Handling of Solution for Injection
Single-use only. Discard any unused portion. If a precipitate has formed as a result of exposure to low temperatures, redissolve by warming to 55°C for no longer than 30 minutes and then shake until the precipitate has dissolved. Allow to cool prior to use.

FOR INTRATHecal USE: DO NOT USE DILUENT CONTAINING BENZYL ALCOHOL. RECONSTITUTE WITH PRESERVATIVE-FREE 0.9 % SODIUM CHLORIDE FOR INJECTION. USE IMMEDIATELY.

Cytarabine is usually administered as a 5 mg/mL concentration in 5 to 15 mL of solution, after an equivalent volume of CSF is removed.

FOR HIGH-DOSE USE: DO NOT USE DILUENT CONTAINING BENZYL ALCOHOL.

Chemical Stability And Compatibility
Stability and Storage Recommendations
Store Cytarabine Injection between 15°C and 25°C. Protect from light.

Cytarabine Injection is supplied in single-use vials. The solution must be used within 24 hours after opening when stored at 15°C to 25°C, and the unused portion discarded.

Further diluted solutions should be used within 24 hours from the time of the initial puncture when stored at 15°C to 25°C or within 72 hours when refrigerated (2°C to 8°C).

Further diluted unpreserved solutions for intrathecal injection must be used immediately, since bacterially contaminated intrathecal solutions could pose very grave risks.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

Cytarabine Injection, when admixed with 0.9% Sodium Chloride Injection to a concentration of 37.5 mg/mL of cytarabine, is chemically stable for a period of 6 days at room temperature, protected from light (refer to WARNING below).

WARNING

a) Although the admixture is chemically stable for up to 6 days when stored at room temperature and protected from light, due to the possibility of microbial contamination during preparation, unpreserved admixtures should be used within
24 hours after preparation when stored at room temperature, or 72 hours when stored under refrigeration.

b) Storage beyond these recommended times should only be permitted if the institution has a recognized intravenous admixture program.

Drug Incompatibilities
Cytarabine is known to be physically incompatible with heparin, insulin, 5-fluorouracil, penicillin G, methyl prednisolone and sodium succinate.

AVAILABILITY OF DOSAGE FORM
Cytarabine Injection is available in single-use vials of 100 mg/mL 1 g/10 mL and 2 g/20 mL.
PART III: CONSUMER INFORMATION

Pr Cytarabine Injection
100 mg/mL

This leaflet is part III of a three-part "Product Monograph" published when Cytarabine Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Cytarabine Injection. Contact a member of your healthcare team if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Cytarabine Injection (Cytarabine) is used alone or in combination with other anticancer medicines in the treatment of patients with certain types of leukemia (cancer of the blood) and lymphomas (cancer of the lymph glands).

What it does:
Cytarabine is a cytotoxic drug that interferes with cell growth and causes cell death.

When it should not be used:
Do not take Cytarabine Injection (Cytarabine) if:
- You are allergic (hypersensitive) to cytarabine or any of the other ingredients in Cytarabine Injection.
- Cytarabine should not be given to premature infants when using a diluent that contains benzyl alcohol.

What the medicinal ingredient is:
Cytarabine.

What the nonmedicinal ingredients are:
Water for injection, may contain hydrochloric acid and/or sodium hydroxide to adjust the pH.

What dosage forms it comes in:
Cytarabine Injection is available in single-use vials of 100 mg/mL, 1 g/10 mL and 2 g/20 mL.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Cytarabine Injection should be used only by doctors with experience in cancer medicines.

Serious side effects with Cytarabine include:
- Decreased production of blood cells (myelosuppression)
- Heart muscle disorders (cardiomyopathy)
- Anaphylactic reactions (exaggerated allergic reaction)
- Tumour Lysis Syndrome (TLS)
- Secondary cancers (other cancers)

In patients on a high-dose schedule of Cytarabine, severe gastrointestinal toxicity, central nervous system toxicity, pulmonary toxicity, at times fatal, and eye toxicity have been reported.

Vaccination with a live vaccine should be avoided while taking Cytarabine Injection.

Cytarabine Injection may cause Tumour Lysis Syndrome [TLS]. TLS is a metabolic condition that results from dying cancer cells and involves changes in blood chemistry that can lead to kidney failure and abnormal heart rhythm, which may be fatal. Tell your doctor immediately if you have palpitations/irregular heartbeats; vomiting; fatigue/weakness; difficulty concentrating/trouble thinking; swelling, numbness or tingling in hands, face or feet; back pain; muscle cramps; fainting or trouble breathing.

Cases of acute pancreatitis, and cases of paralysis, at times fatal in children, have been reported with the use of Cytarabine in combination with other drugs.

Severe nervous system adverse reactions that ranged from headache to paralysis, coma and stroke-like episodes have been reported mostly in children (under 18 years old of age) given intravenous (injected into the vein) cytarabine in combination with intrathecal (injected into the spinal cord) methotrexate.

Tell your doctor before taking Cytarabine Injection, if any of the following apply to you:
- Liver or kidney problems;
- Heart problems;
- Lung problems;
- Low blood cell counts;
- Skin problems;
- Pregnant or think you may be pregnant;
- Breast-feeding;
- Are male patient and plan to father a child.

The safety of Cytarabine Injection in infants (under 1 year of age) is not known.

Contraception
Cytarabine Injection may cause harm to an unborn child. Female patients who might get pregnant must use effective contraception during treatment with Cytarabine Injection. Since Cytarabine Injection may present in the semen, male patients who are not surgically sterile must agree to use effective contraception during treatment with Cytarabine Injection to prevent pregnancy in female partners. If pregnancy is suspected during treatment with Cytarabine Injection, inform your doctor immediately.

Driving and using machines
If you experience dizziness, do not drive or use machinery.

INTERACTIONS WITH THIS MEDICATION
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed, especially the following:
- 5-Fluorocytosine (a medicine used to treat fungal infections);
- Digoxin;
- Gentamicin (an antibiotic);
- Cyclophosphamide, vincristine and prednisone;
- Methotrexate (a medicine used to treat cancer)

PROPER USE OF THIS MEDICATION

Cytarabine Injection Prescribing Information
Cytarabine will be given to you as an injection or an infusion into a vein (through a ‘drip’).

The dose of Cytarabine Injection will be decided by your doctor based on the condition you are being treated for and your body surface area (your body weight and height will be used to calculate your body surface area).

**Overdose**

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional poison control centre, even if there are no symptoms.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Like all medicines, Cytarabine Injection (Cytarabine) can have side effects.

**Tell your doctor or nursing staff immediately,** if you experience the following side effects:
- An allergic reaction such as sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips, rash or itching (especially affecting the whole body), hives;
- Feeling tired;
- Flu-like symptoms, e.g. raised temperature or fever and chills;
- Bruise more easily or bleed more than usual if you hurt yourself.

Other side effects include:
- Reactions at Injection site: inflammation to your veins (caused by a blood clot) and infection;
- Headaches or feeling dizzy, feeling of pins and needles, shaking and fits, drowsiness, experience problems in walking, speech problems, involuntary muscular movement, changes in your personality, tiredness, weakness, fainting;
- Hair loss, a skin rash or ulceration, peeling of the skin, itching or increased freckles;
- Infections;
- Feeling sick, being sick, diarrhea, loss of appetite, abdominal pain, abdominal swelling and bloody stool;
- Inflammation of the gullet, heartburn, sores and bleeding in the mouth, lips, or on the anus (back passage);
- Pancreatitis (pain in the upper abdomen) often accompanied by feeling sick or vomiting;
- Liver damage (seen as yellowing of the skin and whites of the eye);
- Difficulty or pain when passing urine, blood in your urine and impaired kidney function;
- Feeling hot and feverish, conjunctivitis, and pain and numbness in joints, fingers, toes or face, swelling of the abdomen, legs, ankles and feet;
- Paralysis;
- Shortness of breath, pneumonia, short or stabbing chest pain, build up of fluid in the lungs, sore throat;
- Muscle pain, bone pain;
- Fast heart beat;
- Eye infection, irritation, pain and blurred vision, visual loss, intolerance to light;
- Cytarabine Syndrome can happen between 6 to 12 hours after receiving Cytarabine. The syndrome includes feeling generally unwell with a high temperature, pain in bone, muscle and sometimes the chest, blistery rash, sore eyes.
- Rash or blisters on the palms of the hands and soles of the feet.

If any of the side effects get serious or if you notice any side effect not listed in this leaflet, please tell your doctor or nursing staff immediately.

**SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

<table>
<thead>
<tr>
<th>Symptom / Effect</th>
<th>Talk with your doctor or pharmacist</th>
<th>Stop taking the drug and call your doctor or pharmacist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis (inflammation of the pancreas) with symptoms such as abdominal pain, fever, nausea, vomiting</td>
<td>Only if severe</td>
<td>Yes</td>
</tr>
<tr>
<td>Decreased white blood cell and platelet counts with symptoms such as infection, fever, bleeding, bruising and rash</td>
<td>In all cases</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*This is not a complete list of side effects. For any unexpected effects while taking Cytarabine Injection, contact your doctor or pharmacist.*
HOW TO STORE IT

Store Cytarabine Injection between 15°C and 25°C. Protect from light.

The solution must be used within 24 hours after opening when stored at 15°C to 25°C, and the unused portion discarded.

Further diluted solutions should be used within 24 hours from the time of the initial puncture when stored at 15°C to 25°C or within 72 hours when refrigerated (2°C to 8°C).

Further diluted unpreserved solutions for intrathecal injection must be used immediately, since bacterially contaminated intrathecal solutions could pose very grave risks.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

Cytarabine Injection, when admixed with 0.9% Sodium Chloride Injection to a concentration of 37.5 mg/mL of cytarabine, is chemically stable for a period of 6 days at room temperature, protected from light (refer to WARNING below).

WARNING

a) Although the admixture is chemically stable for up to 6 days when stored at room temperature and protected from light, due to the possibility of microbial contamination during preparation, unpreserved admixtures should be used within 24 hours after preparation when stored at room temperature, or 72 hours when stored under refrigeration.

b) Storage beyond these recommended times should only be permitted if the institution has a recognized intravenous admixture program.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, ON K1A 0K9

Postage-paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Hospira Healthcare Corporation at 1-866-488-6088, Option 4.

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