Cytarabine Injection BP 100 mg/1mL, 500 mg/5 mL, 1000 mg/10 mL & 2000 mg/20 mL

Cytalon™ 100/500/1000/2000

Rx only

COMPOSITION

Cytalon™ 100

Cytarabine Injection BP 100 mg/1mL

Each mL contains

Cytarabine IP	100mg
Sodium Hydroxide IP	q.s.
Hydrochloric Acid IP	q.s.
Water for Injections IP	q.s.

Cytalon™ 500

Cytarabine Injection BP 500 mg/5 mL

Each mL contains

Cytarabine IP	100mg
Sodium Hydroxide IP	q.s.
Hydrochloric Acid IP	q.s.
Water for Injections IP	q.s.

Cytalon™ 1000

Cytarabine Injection BP 1000 mg/10 mL

Each mL contains

Cytarabine IP	100mg
Sodium Hydroxide IP	q.s.
Hydrochloric Acid IP	q.s.
Water for Injections IP	q.s.

Cytalon™ 2000

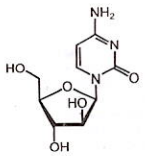
Cytarabine Injection BP 2000 mg/20 mL

Each mL contains

Cytarabine IP	100mg
Sodium Hydroxide IP	q.s.
Hydrochloric Acid IP	q.s.
Water for Injections IP	q.s.

DESCRIPTION

Cytarabine Injection BP 100mg/mL, 500mg/5 mL, 1000mg/10mL & 2000mg/20 mL is a clear colorless solution filled in 3mL, 5mL, 10mL & 20mL vials. Cytarabine is an odorless, white to off-white, crystalline powder which is freely soluble in water and slightly soluble in alcohol and in chloroform. Cytarabine is chemically 4-amino-1-β-D-arabinofuranosyl-2(1H)-pyrimidinone. Its molecular formula is: $C_9H_{13}N_3O_5$. and Molecular Weight is 243.22. The structural formula is:



CLINICAL PHARMACOLOGY

Cytarabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G_1 phase to the S-phase. Although the mechanism of action is not completely understood, it appears that cytarabine acts through the inhibition of DNA polymerase. Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate, an effective inhibitor of DNA polymerase. It is inactivated by a pyrimidine nucleoside deaminase. The balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine. Cytarabine brings about extensive chromosomal damage, including chromatoid breaks, Cytarabine may also incorporate into both DNA and RNA.

Cytarabine is rapidly metabolized and is not effective when taken 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. The 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. Within 24 hours, about 80% of the administered radioactivity can be recovered in the urine, approximately 90% of which is excreted as ara-U (Inactive metabolite). Relatively constant plasma levels can be achieved by continuous intravenous infusion. After subcutaneous or intramuscular administration of cytarabine peak plasma levels are achieved about 20 to 60 minutes after injection. Cerebrospinal fluid levels of cytarabine are low in comparison to plasma levels after single intravenous injection because cerebrospinal fluid levels of deaminase are low. Cytarabine also has shown immunosuppressive activity during administration with little or no accompanying toxicity.

INDICATIONS

Cytarabine Injection in combination with other approved anticancer drugs is indicated for remission induction in acute non-lymphocytic leukemia of adults and pediatric patients. It has also been found useful in the treatment of acute lymphocytic leukemia and the blast phase of chronic myelocytic leukemia. Intrathecal administration of Cytarabine Injection is indicated in the prophylaxis and treatment of meningeal leukemia.

CONTRAINDICATIONS

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

WARNINGS

Myelosuppression

Cytarabine is a potent bone marrow suppressant. 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. Patients may suffer from severe infections due to bone marrow suppression like infection resulting from granulocytopenia and other impaired body defenses, and hemorrhage secondary to thrombocytopenia.

Ocular Toxicity

Reversible corneal toxicity and hemorrhagic conjunctivitis may occur while on treatment with cytarabine. This may be prevented or diminished by prophylaxis with a local corticosteroid eye drop.

CNS Toxicity

Cerebral and cerebellar dysfunction, including personality changes, somnolence and coma, usually reversible.

GI Toxicity and Hepatic Dysfunction

Severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis leading to peritonitis; sepsis and liver abscess; liver damage with increased hyperbilirubinemia; bowel necrosis; and necrotizing colitis.

Dermatologic Toxicity

Though 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. If experimental high-dose therapy is used, avoid using a diluent containing benzyl alcohol.

Cardiac Toxicity

Cases of cardiomyopathy with subsequent death have been reported following experimental high-dose therapy with cytarabine in combination with cyclophosphamide when used for bone marrow transplant preparation.

Pulmonary Toxicity

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

Use in Pregnancy

Cytarabine can cause fetal harm when administered to a pregnant woman. Cytarabine causes abnormal cerebellar development in the neonatal hamster and is teratogenic to the rat fetus. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General: Frequent platelet and leukocyte counts and bone marrow examinations are mandatory. Dose modification is required when drug-induced marrow depression has resulted in a platelet count under 50,000/mm^3 or a polymorphonuclear granulocyte count under 1000/mm^3. Peripheral blood cell count may continue to fall after the drug is stopped and reach lowest values after drug-free intervals of 12 to 24 days. When indicated, restart therapy when definite signs of marrow recovery appear (on successive bone marrow studies). The human liver apparently detoxifies a substantial fraction of an administered dose. In particular, patients with renal or hepatic function impairment may have a higher likelihood of CNS toxicity after high-dose cytarabine treatment. Use the drug with caution and possibly at reduced dose in patients whose liver or kidney function is poor. Acute pancreatitis has been reported to occur in a patient receiving cytarabine by continuous infusion and in patients being treated with cytarabine who have had prior treatment with L-asparaginase.

Emetogenicity: 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.

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

Carcinogenesis, Mutagenesis and Impairment of Fertility

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

Usage in Pregnancy

"Pregnancy Category D."

Nursing Mothers

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.

For the use only of a Registered Medical Practitioner / Oncologist or a Cancer Hospital or a Laboratory

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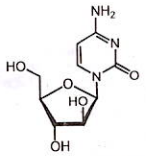

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