INJECTION

# CYTOCIN 100mg , 500mg

## B.P Specs.

## (CYTARABINE B.P)

انجکشن

## سائٹوسن 100 ملی گرام، 500 ملی گرام

(سائیٹرابن) بی۔پی

**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 nontoxic 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 i.v. injection, 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-b-D-arabinofuranosyluracid (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 s.c. or i.m. administration, peak plasma levels of radioactivity are achieved about 20 to 60 minutes after injection and are considerably lower than those after i.v. administration. Cerebrospinal fluid levels of cytarabine are low in comparison to plasma levels after single i.v. injection. However, in one patient in whom cerebrospinal levels were examined after 2 hours of constant i.v. 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.

**Caution:** Cytarabine is a potent drug and should be used only by physicians experienced with cancer therapeutic drugs (see Warnings and Precautions). Hematologic, renal and hepatic evaluations must be done at regular intervals.

**Indications and Clinical Uses:** Induction and maintenance of remission in acute leukemia in children and adults. 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 nonHodgkin'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/mas an i.v. 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.

**Acute Myelocytic Leukemia:** Tables I and II 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.

**Acute Lymphocytic Leukemia:** 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. Tables III and IV 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.

**Intrathecal Use in Meningeal Leukemia:** Cytarabine has been used intrathecally in acute leukemia in doses ranging from 5 to 75 mg/mof 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/mevery 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 CNS manifestations and the response to previous therapy. Cytarabine has been used intrathecally with hydrocortisone sodium succinate 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/m hydrocortisone sodium succinate 15 mg/m and methotrexate 15 mg/m 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. Focal leukemic involvement of the CNS 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.

**NonHodgkin's Lymphoma in Children:** Cytarabine has been used as part of a multidrug program (LSA2L2) to treat NonHodgkin's lymphoma in children.

**Contra-Indications:** Patients who are hypersensitive to the drug.

**Manufacturers' Warnings In Clinical States:** 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. Facilities should be available for management of complications (possibly fatal) of bone marrow suppression (infection resulting from granulocytopenia and other impaired body defences, and hemorrhage secondary to thrombocytopenia). Severe and at times fatal, CNS, gastrointestinal and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following high dose schedules (2 to 3 g/m of cytarabine. These reactions include reversible corneal toxicity and hemorrhagic conjunctivitis; which may be prevented or diminished by prophylaxis with a local corticosteroid eye drop; cerebral and cerebellar dysfunction including personality changes, somnolence and coma, usually reversible; severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis, leading to peritonitis; sepsis and liver abscess; pulmonary edema; liver damage with increased bilirubin; bowel necrosis; and necrotizing colitis. Two patients treated with conventional doses of cytarabine sterile powder and daunomycin developed abdominal tenderness (peritonitis) and guaiac positive colitis. Both patients responded to nonoperative medical management. Both patients exhibited neutropenia and thrombocytopenia and were receiving numerous other drugs. The authors recommend careful, conservative management in patients receiving cytarabine who appear to have a surgical abdomen, but in whom a definitive surgical diagnosis cannot be made. Two patients with childhood acute myelogenous leukemia who received intrathecal and i.v. cytarabine at conventional doses, in addition to a number of other concomitantly administered drugs, developed delayed progressive ascending paralysis resulting in death in one of the two patients. Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more commonly seen with high-dose therapy than with standard treatment programs. If high-dose therapy is used, do not use a diluent containing benzyl alcohol. Benzyl alcohol is contained in the diluent for this product. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. 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. 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 from one institution in 16/72 patients. In one case, the outcome was fatal. Acute pancreatitis has been reported to occur in patients being treated with cytarabine in combination with other drugs. Extensive chromosomal damage, including chromatoid breaks have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported.

**Pregnancy:** 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. 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 7 infants with various problems in the neonatal period, including pancytopenia; transient depression of WBC, hematocrit or platelets; electrolyte abnormalities; transient eosinophilia; and one case of increased IgM levels and hyperpyrexia possibly, due to sepsis. Six of the 7 infants were also premature. The child with pancytopenia died at 21 days of sepsis. Therapeutic abortions were done in 5 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 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.

**Lactation:** 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.

**Precautions:** Patients receiving 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 1 000/mm Counts of formed elements in the peripheral blood may continue to fall after the drug is stopped and reach lowest values after drug-free intervals of 12 to 24 days. When indicated, restart therapy when definite signs of marrow recovery appear (on successive bone marrow studies). Patients whose drug is withheld until "normal" peripheral blood values are attained, may escape from control. When large i.v. 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. The human liver apparently detoxifies a substantial fraction of an administered cytarabine dose. 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.

**Children:** The safety of the drug for use in infants is not established. 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.

**Adverse Reactions:** 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/mto 600 mg/m 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. A syndrome has been described which 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.

**The following additional adverse reactions have been reported:** anorexia, nausea, vomiting, diarrhea, oral and anal inflammation or ulceration, nausea and vomiting following rapid i.v. injection, rash, hepatic dysfunction, fever, thrombophlebitis, bleeding (all sites), sepsis, pneumonia, cellulitis at injection site, skin ulceration, urinary retention, renal dysfunction, neuritis, neural toxicity, sore throat, esophageal ulceration, esophagitis, chest pain, bowel necrosis, abdominal pain, freckling, jaundice, conjunctivitis (may occur with rash), dizziness, alopecia, anaphylaxis, allergic edema, pruritus, shortness of breath, urticaria and headache.

**High-Dose Therapy:** Severe and at times fatal CNS, gastrointestinal and pulmonary toxicity have been reported following high dose schedules (2 to 3 g/mevery 12 hours for 12 doses). These reactions include reversible corneal toxicity and hemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with a local corticosteroid eyedrop; cerebral and cerebellar dysfunction including personality changes, somnolence and coma, usually reversible; severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis leading to peritonitis; sepsis and liver abscess; pulmonary edema; liver damage with increased bilirubin; bowel necrosis; and necrotizing colitis. Two patients with adult acute non-lymphocytic leukemia developed peripheral motor and sensory neuropathies after consolidation with high-dose cytarabine, daunorubicin, and asparaginase. Patients treated with high-dose cytarabine should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurologic disorders. Ten patients treated with experimental intermediate doses of cytarabine (1 g/m with and without other chemotherapeutic agents (meta-AMSA, daunorubicin, VP-16) developed a diffuse interstitial pneumonitis without clear cause that may have been related to the cytarabine. Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more commonly seen with high dose therapy than with standard treatment programs. If high dose therapy is used, do not use a diluent containing benzyl alcohol. 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 occurred in 5 children; these patients had also been treated with intrathecal methotrexate and hydrocortisone, as well as by CNS radiation. Isolated neurotoxicity has been reported. Blindness occurred in 2 patients in remission whose treatment had consisted of combination systemic chemotherapy, prophylactic CNS radiation and intrathecal cytarabine. Corneal toxicity consisting of ocular pain, tearing, foreign-body sensation, photophobia and blurred vision have been reported. One case of anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation has been reported. This
occurred immediately after the i.v. administration of cytarabine.

**Symptoms and Treatment of Overdose:** Symptoms and Treatment: There is no antidote for cytarabine overdosage. 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 overdosage may cause serious bone marrow suppression. Daily hematological evaluation should be performed to prevent overdosage. Nausea and vomiting, although a general side effect of the drug, may be an additional warning ofoverdosage. Severe hemorrhage into the gastrointestinal tract may indicate overdosage given overdosage. Severe hemorrhage into the gastrointestinal tract may indicate overdosage 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 g/mi.v. infusion over 1 hour every 12 hours for 12 doses and 3 g/mcontinuous infusion for 4 days, other than reversible bone marrow suppression has been reversible corneal, cerebral and cerebellar dysfunction. Doses of 4.5 g/mi.v. infusion over 1 hour every 12 hours for 12 doses has caused an unacceptable increase in irreversible toxicity and death.

**Dosage and Administration:** Caution: The following precautionary measures are recommended in proceeding with the preparation and handling of cytotoxic agents such as cytarabine: The procedure should be carried out in a vertical laminar flow hood (Biological Safety Cabinet - Class II). Personnel should wear: PVC gloves, safety glasses, disposable gowns and masks. 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. 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 i.v. infusion, injection/s.c. or intrathecally. Thrombophlebitis has occurred at the site of drug injection or infusion in some patients, and rarely patients have noted pain and inflammation at s.c. 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 i.v. injection as compared with slow infusion. This phenomenon is related to the drug's rapid inactivation and brief exposure of susceptible normal and neoplastic cells to significant levels after rapid injection. Normal and neoplastic cells seem to respond in somewhat parallel fashion to these different modes of a dministration 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 i.v. 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.

**Acute Myelocytic Leukemia:** Induction remission: Adults: 200 mg/mdaily by continuous infusion for 5 days (120 hours). Total dose 1 000 mg/m This course is repeated approximately every 2 weeks. Modifications must be made based on hematologic response. Meningeal Leukemia: Intrathecal Use: (see Indications and Warnings).

**Dosage Modification:** The dosage of 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 1 000 polymorphonuclear granulocytes/mmin 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 escaoe of the patient's disease from control by the drug.

**Intrathecal Use in Meningeal Leukemia:** Cytarabine has been used intrathecally in acute leukemia in doses ranging from 5 mg/mto 75 mg/mof 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/mevery 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 CNS manifestations and the response to previous therapy. Cytarabine has been used intrathecally with hydrocortisone sodium succinate 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/m hydrocortisone 15 mg/m and methotrexate 15 mg/m 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 antileukemia 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 CNS radiation. Isolated neurotoxicity has been reported. Blindness occurred in 2 patients in remission whose treatment had consisted of combination systemic chemotherapy, prophylactic CNS radiation and intrathecal cytarabine. Focal leukemic involvement of the CNS may not respond to intrathecal cytarabine and may better be treated with radiotherapy.

Intrathecal Use: If solutions are used intrathecally, do not use a diluent containng benzyle alcohol. Reconsititute with preservative-free 0.9% Sodium Chloride for Injection. Use immediately

High-dose Use: Do not use diluent containing benzyle alcohol.

Chemical Stability and Compatability: Cytarabine is compatible for 24 hours at 5 C with Dextrose 5% in Water. 0.9% Sodium chloride, Dextrose 5% in Water with 0.9% Sodium chloride. Cytarabine 0.8mg/mL and sodium cephatothin 1.0 mg/mL are chemically. Cytarabine 0.4 mg/mL and prednisolone sodium phosphate 0.2 mg/mL are compatible in dextrose 5% in water for 8 hours. Cytarabine 16 ug/m: and vincristine sulfate 4 4 ug/mL are compatible in doxtrose 5% in water for 8 hours. Cytarabine has been known to be physically incompatible with heparin, insulin , methotrexate, 5-fluorouracil, pencillin G, and methyprednisolone sodium succinate. As with all i.v. admixtures, dilution should be made just prior to administration and the resulting unpreserved solution used within 24 hours.

Reconstitution: Cytarabine sterile powder may be reconstituted with the follwoing dilunets: 0.9% Sodium chloride for injection, Dextrose 5% in Water, Sterile water for injection, Bacteriostatic water for injection. pH of reconstituted solution is 7.0 to 9.5 approximately. Solutions reconstituted should be used immediately.

Availability: Cytocin-100 Injection:
Each vial contains sterile cytarabine B.P 100mg packed in unit carton along with 5ml ampoule of sterile water for injection B.P as solvent.

Cytocin-500 Injection:
Each vial contains cytarabine B.P 500mg packed in unit carton along with ampoule of sterile water for injection B.P as solvent.

Dosage: As directed by the physician.

Instructions: Store at 15 to 30 C̊. Protect from heat, light and moisture.

Keep all medicines out of the reach of children.

To be sold on prescription of registered medical practitioner.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: 15 سے 30 ڈگری سینٹی گریڈ پر رکھیں۔ گرمی، نمی اور روشنی سے بچائیں۔ تمام ادویات

بچوں کی پہنچ سے دور رکھیں۔ صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

**Manufactured by:**
**PHARMEDIC LABORATORIES (PVT) LIMITED.**
**16 Km. Multan Road, Lahore - Pakistan**