
DATA SHEET

CYTRACCORD

NAME OF MEDICINE

Cytarabine Injection BP 100 mg/mL

PRESENTATION

Cytarabine Injection is a sterile, preservative-free solution containing Cytarabine Macrogol 400 and Trometamol in Water for Injections BP.

The product is a clear, colourless solution, which is practically free from particles.

USES

Actions

Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Although the mechanism of action is not completely understood, it appears that cytarabine acts through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. Extensive chromosomal damage, including chromatoid breaks, has been produced by cytarabine and malignant transformation of rodent cells in culture has been reported. Deoxycytidine prevents or delays (but does not reverse) the cytotoxic activity.

Cell culture studies have shown an antiviral effect. However, efficacy against *herpes zoster* or smallpox could not be demonstrated in controlled clinical trials.

In experimental studies with mouse tumours, cytarabine was most effective in those tumours with a high growth fraction. The effect was dependent on the treatment schedule; optimal effects were achieved when the schedule (multiple, closely spaced doses or constant infusion) ensured contact of the drug with the tumour cells when the maximum number of cells were in the susceptible S-phase. The best results were obtained when courses of therapy were separated by intervals sufficient to permit adequate host recovery.

Pharmacokinetics

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 deaminate which converts it to the nontoxic uracil derivative. It

appears that the balance of kinase and deaminate levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine.

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

Following rapid intravenous injection of cytarabine labelled with tritium, the disappearance from plasma is biphasic. There is an initial distributive phase with half-life of about ten minutes, followed by a second elimination phase with a half-life of about one to three hours.

After the distributive phase, over 80 percent of plasma radioactivity can be accounted for by the inactive metabolite 1- β -D-arabino-furanosyluracil (ara-U). Within 24 hours about 80 percent of the administered radioactivity can be recovered in the urine, approximately 90 percent of which is excreted as ara-U.

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

After subcutaneous or intramuscular administration of cytarabine labelled with tritium, 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 two hours of constant intravenous infusion, levels approached 40 percent of the steady state plasma level. With intrathecal administration, levels of cytarabine in the cerebrospinal fluid declined with a first order half-life of about two hours. Because cerebrospinal fluid levels of deaminate are low, little conversion to ara-U was observed.

Immunosuppressive action: Cytarabine is capable of obliterating immune responses in man during administration with little or no accompanying toxicity. Suppression of antibody responses to E.coli-V1 antigen and tetanus toxoid have been demonstrated. This suppression was obtained during both primary and secondary antibody responses.

Cytarabine also suppressed the development of cell-mediated immune responses such as delayed hypersensitivity skin reaction to dinitrochlorobenzene. However, it had no effect on already established delayed hypersensitivity reactions.

Following 5-day courses of intensive therapy with cytarabine the immune response was suppressed, as indicated by the following parameters: macrophage ingress into skin windows; circulating antibody response following primary antigenic stimulation; lymphocyte blastogenesis with phytohaemagglutinin. A few days after termination of therapy there was a rapid return to normal.

Indications

Cytarabine is indicated primarily for induction and maintenance of remission in acute myelocytic leukaemia of both adults and children. It has also been found to be useful in the

treatment of other leukaemias such as acute lymphocytic leukaemia, chronic myelocytic leukaemia (blast phase) and erythroleukemia. Cytarabine may be used alone or in combination with other antineoplastic agents; the best results are often obtained with combination therapy.

Cytarabine has been used experimentally in a variety of neoplastic diseases. In general, few patients with solid tumors have benefitted.

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

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

DOSAGE AND ADMINISTRATION

Cytarabine may be administered by intravenous injection or infusion, or subcutaneously. 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.

N.B.: Cytarabine Injection 100 mg/mL is hypertonic and therefore unsuitable for intrathecal use.

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

Dose regimens are usually at the discretion of the attending physician. Clinical and haematological responses and tolerance vary between patients and a dose which gives optimal therapeutic effect with minimum toxicity should be used.

In many chemotherapeutic programmes, Cytarabine is used in combination with other cytotoxic drugs. The addition of these cytotoxic drugs has necessitated changes and dose alterations.

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

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

Cytarabine 200 milligrams/m² daily by continuous IV infusion over 24 hours for 5 days (120 hours) - total dose 1000 milligrams/m². The course is repeated approximately every 2 weeks. Modifications based on haematologic response should be made.

Combined Chemotherapy:

Before instituting a programme 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 programme.

Cytarabine, Doxorubicin

Cytarabine: 100 milligrams/m²/day, continuous IV infusion (days 1 to 10)

Doxorubicin: 30 milligrams/m²/day, IV infusion of 30 minutes (days 1 to 3)

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

Cytarabine, Thioguanine, Daunorubicin

Cytarabine: 100 milligrams/m²/day, IV infusion over 30 minutes every 12 hours (days 1 to 7)

Thioguanine: 100 milligrams/m², orally every 12 hours (days 1 to 7)

Daunorubicin: 60 milligrams/m²/day, IV infusion (days 5 to 7)

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

Cytarabine, Doxorubicin, Vincristine, Prednisolone

Cytarabine: 100 milligrams/m²/day, continuous IV infusion (days 1 to 7)

Doxorubicin: 30 milligrams/m²/day, IV infusion (days 1 to 3)

Vincristine: 1.5 milligrams/m²/day, IV infusion (days 1 to 5)

Prednisolone: 40 milligrams/m²/day, IV infusion every 12 hours (days 1 to 5)

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

Cytarabine, Daunorubicin, Thioguanine, Prednisone, Vincristine

Cytarabine: 100 milligrams/m²/day, IV every 12 hours (days 1 to 7)

Daunorubicin: 70 milligrams/m²/day, IV infusion (days 1 to 3)

Thioguanine: 100 milligrams/m² orally (days 1 to 7)

Prednisone: 40 milligrams/m²/day, orally (days 1 to 7)

Vincristine: 1 milligram/m²/day, IV infusion (days 1,7)

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

Cytarabine, Daunorubicin

Cytarabine: 100 milligrams/m²/day, continuous IV infusion (days 1 to 7)

Daunorubicin: 45 milligrams/m²/day, IV push (days 1 to 3)

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

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

Acute myelocytic leukaemia-induction and maintenance in 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 lymphocytic leukaemia: In general, dosage schedules are similar to those used in acute myelocytic leukaemia with some modifications.

Dosage modification: The dosage of Cytarabine must be modified or suspended when signs of serious haematologic depression appear. In general, consider discontinuing the drug if the patient has less than 50,000 platelets or 1000 polymorphonuclear granulocytes/mm³ in their 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.

CONTRAINDICATIONS

Known hypersensitivity to cytarabine.

WARNINGS AND PRECAUTIONS

Cytarabine is a potent bone marrow suppressant. Patients receiving the drug must be kept under close medical supervision. Leucocyte and platelet counts should be performed daily and frequent bone marrow examinations conducted. Facilities should be available for management of complications of bone marrow suppression.

Cytarabine Injection 100 milligrams per mL (ready prepared solution) is hypertonic and therefore is unsuitable for intrathecal use.

Two patients with childhood acute myelogenous leukaemia who received intrathecal and intravenous 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.

Cytarabine should only be used under constant supervision by physicians experienced in therapy with cytotoxic agents.

Hyperuricaemia secondary to rapid lysis of neoplastic cells may occur in patients receiving cytarabine; serum uric acid concentrations should be monitored.

Periodic determinations of renal and hepatic function should also be performed.

Use the drug with caution and at reduced doses in patients whose liver function is poor as the liver apparently detoxifies a substantial fraction of an administered dose.

Acute pancreatitis has been reported to occur in patients being treated with cytarabine who have had prior treatment with L-asparaginase.

Patients treated with high dose cytarabine should be observed for neuropathy since dose schedule alteration may be needed to avoid irreversible neurological disorders.

Use in Children

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

Use in the Elderly

Although studies with cytarabine have not been performed in the geriatric population, geriatric-specific problems that would limit the usefulness of this medication in the elderly are not expected. Elderly patients are, however, more likely to have age-related renal function impairment, which may require reduction of dosage in patients receiving cytarabine.

Mutagenicity

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

Carcinogenicity

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

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

Pregnancy and Lactation

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

Use in lactation It is not known whether cytarabine is excreted in human milk. Women should be advised not to breast feed while being treated with cytarabine, because of the risks to the infant (see Adverse Effects, Mutagenicity, Carcinogenicity).

Effects on ability to drive and use machines.

Cytarabine for Injection is likely to produce severe adverse effects, which may impair the patient's ability to concentrate and react and therefore constitute a risk in the ability to drive and use machines.

ADVERSE EFFECTS

The major adverse effect of cytarabine is haematologic toxicity. Myelosuppression is normally manifested by megaloblastosis, leucopenia, anaemia, reticulocytopenia and thrombocytopenia. Leucopenia follows mainly from granulocyte depression; lymphocytes are minimally affected. The severity of these adverse effects is dependent on the dose of the drug and schedule of administration.

Granulocytopenia is biphasic, with a nadir at 7 to 9 days after a dose and another, more severe, at 15 to 24 days. The nadir of the platelet count occurs at about 12 to 15 days. Recovery generally occurs in a further ten days.

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

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

Other adverse effects of the GI tract include anorexia, diarrhoea, and oral and anal inflammation or ulceration. Abdominal pain, oesophagitis, sore throat, oesophageal ulceration, and GI haemorrhage occur less frequently. In one study, cytarabine has been reported to induce severe intestinal toxicity when used in several sequential chemotherapeutic protocols. The mucosal alterations induced were characterised by surface and glandular epithelial atypia, immaturity and necrosis. These were associated with diarrhoea, ileus, abdominal pain, haematemesis and melaena, severe hypokalaemia, hypocalcaemia, a protein-losing enteropathy, transient weight gains and intestinal infections.

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

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

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

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

Blindness occurred in 2 patients with ALL during remission, who had received systemic combination therapy, prophylactic CNS radiation as well as intrathecal cytarabine. Necrotizing leucoencephalopathy has been reported to have occurred in 5 children who had received triple intrathecal therapy consisting of cytarabine, methotrexate and hydrocortisone, and CNS irradiation.

Other reported adverse effects of cytarabine include fever, rash, conjunctivitis (may occur with rash), alopecia, freckling, skin ulceration, urinary retention, renal dysfunction, chest pain, dizziness, somnolence, neuritis or neural toxicity and reactions at the site of injection such as pain, inflammation, thrombophlebitis, or cellulitis.

One patient suffered anaphylaxis with acute cardiopulmonary arrest which required resuscitation, immediately following IV administration of the drug.

A cytarabine syndrome characterised by fever, myalgia, bone pain, malaise, maculopapular rash, conjunctivitis, and occasionally chest pain, has been reported. A "flu-like" syndrome has been reported, which may be treated with corticosteroid therapy if severe. Anaphylactoid reactions have occurred.

It normally occurs at 6 to 12 hours after administration of the drug; corticosteroids have been shown to be of benefit in the treatment and prevention of the syndrome. If treatment of the symptoms of the syndrome is required, administration of corticosteroids should be considered, as well as continuation of cytarabine therapy.

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

Although doses exceeding recommended dosage schedules have been used clinically and have been tolerated, severe and at times fatal adverse effects have been associated with high-dose cytarabine regimens (2.0 g to 3.0 g/m² given every 12 hours for 12 doses). These include cerebral and cerebellar dysfunction including personality changes, somnolence and coma which is generally reversible; conjunctivitis and reversible corneal toxicity (keratitis) consisting of ocular pain, tearing, foreign-body sensation, photophobia and blurred vision; pulmonary oedema and severe GI ulceration including pneumatosis cystoides intestinalis leading to peritonitis, sepsis and liver abscess; liver changes, necrotising colitis and bowel necrosis. Severe skin rash leading to desquamation, alopecia and cardiac disorders has also been reported.

Doses of 4.5 g/m² IV infusion over 1 hour every 12 hours for 12 doses have caused an unacceptable increase in irreversible toxicity and even death.

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

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary oedema and radiologically pronounced cardiomegaly has been reported following experimental high dose therapy of cytarabine for relapsed leukaemia. This syndrome can have fatal consequences.

INTERACTIONS

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

Use with care following prior treatment with L-asparaginase (see **Warnings and Precautions**)

- *Flucytosine* should not be administered concomitantly with cytarabine. Cytarabine has been reported to antagonise the antifungal activity of flucytosine by competitive inhibition.
- *Allopurinol, Colchicine, Probenecid or Sulphinpyrazone*: Cytarabine may raise the concentration of blood uric acid. Dosage adjustment of antigout agents may be necessary to control hyperuricaemia and gout. Allopurinol may be preferred to prevent or reverse cytarabine-induced hyperuricaemia because of risk of uric acid nephropathy with uricosuric antigout agents.
- *Blood Dyscrasia Causing Medications*: Leukopenic and/or thrombocytopenic effects of cytarabine may be increased with concurrent or recent therapy if these medications cause the same effects, dosage adjustment of cytarabine, if necessary, should be based on blood counts.
- *Bone Marrow Depressants or Radiation Therapy*: Additive bone marrow depression may occur; dosage reduction may be required when two or more bone marrow depressants, including radiation, are used concurrently or consecutively.
- *Cyclophosphamide*: Concurrent use with high-dose cytarabine therapy for bone marrow transplant preparation has been reported to result in an increase in cardiomyopathy with subsequent death.
- *Methotrexate*: Cytarabine has been reported to inhibit the cellular uptake of methotrexate, thus reducing its effectiveness. Conversely, methotrexate has been reported to decrease the intracellular activation of cytarabine. These factors should be considered when using the medicines concurrently.

OVERDOSAGE

Severe bone marrow depression, gastrointestinal toxicity and vomiting are among the signs and symptoms expected. Treatment with cytarabine should be ceased and supportive measures instituted. In bone marrow depression, transfusions of blood products may be required and active measures may be necessary to combat infection.

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

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

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

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

PHARMACEUTICAL PARTICULARS

List of excipients

Macrogol 400
Trometamol
Water for Injections

Incompatibilities

Incompatibilities with: Heparin, insulin, Methotrexate, 5-fluorouracil, nafcillin, oxacillin, penicillin G, methyl-prednisolone succinate.

Shelf life of the product as package for sale:

2 years

Shelf life after first opening the container:

The vials are for single use only and any unused portion must be discarded after use. From a microbiological point of view, the product should be used immediately after the first penetration of the rubber stopper. If not used immediately, in use storage times and conditions are the responsibility of the user.

Shelf life after dilution of the solution for injection:

Cytarabine 100 mg/ml Injection may be further diluted, under aseptic conditions, in dextrose injection (5% w/v) or sodium chloride injection (0.9 % w/v) or water for injection and administered as an intravenous infusion.

In use stability: Chemical and physical in-use stability has been demonstrated in sodium chloride injection (0.9 % w/v) and dextrose injection (5% w/v) for up to 24 hours at temperature below 25° C and for up to 72 hours at 2-8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8° C, unless dilution has taken place in controlled and validated aseptic conditions.

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

Special precautions for storage

Store below 25° C. Do not refrigerate. Keep the vial in the outer carton in order to protect from light.

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

Nature and contents of container

For 1 ml,

Solution for injection is filled in 2 ml Type - I clear glass vial closed with 13 mm grey rubber stopper and 13 mm aluminium flip-off transparent blue seal.

For 5 ml,

Solution for injection is filled in 5 ml Type - I clear tubular glass vial closed with 20 mm grey rubber stopper and 20 mm aluminium flip-off transparent blue seal.

For 10 ml,

Solution for injection is filled in 10 ml Type - I clear tubular glass vial closed with 20 mm grey rubber stopper and 20 mm aluminium flip-off transparent blue seal.

Pack sizes:

1 × 1 ml vial, 5 × 1 ml vial

1 × 5 ml vial, 5 × 5 ml vial

1 × 10 ml vial

MEDICINE CLASSIFICATION

Prescription Medicine.

FURTHER INFORMATION**Handling precautions**

As with all antineoplastic agents, trained personnel should prepare Cytarabine Injection. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling cytarabine. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as cytarabine.

Luer-Lock fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.

Items used to prepare cytarabine, or articles associated with body waste, should be disposed of by placing in a double sealed polythene bag and incinerating at 1100°C.

Spills and disposal

If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with a suitable material such as absorbent towel or adsorbent granules. Spills may also be treated with 5% sodium hypochlorite. Collect up absorbent/adsorbent material and

other debris from spill and place in a leak proof plastic container and label accordingly. Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled 'CYTOTOXIC WASTE FOR INCINERATION AT 1100°C'. Waste material should be incinerated at 1100°C for at least 1 second. Cleanse the remaining spill area with copious amounts of water.

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