ARASID INJECTION BP 100MG/ML
(Cytarabine Injection BP 100mg/ml; 1 ml, 5 ml & 10ml)

Name and strength of active ingredient

Cytarabine Ph.Eur. 100 mg/mL

Dosage form

Injection

Product Description

A clear, colourless solution filled in a clear glass vial. When examined under suitable conditions of visibility it should be practically free from particles.

Pharmacodynamic properties

Cytarabine is metabolised *in vivo* to ARA-CTP phosphorylated compound. This competitively inhibits DNA polymerase and may also inhibit certain acid kinase enzymes. Primarily the drug acts as a false nucleoside and competes for enzymes involved in the conversion of cytidine nucleotide to deoxycytidine nucleotide and also incorporation into the DNA.

Cytarabine has no effect on non proliferating cells nor on proliferating cells unless in the S phase. It is a cell cycle specific antineoplastic drug.

Pharmacokinetic properties

Oral administration is ineffective due to rapid deamination in the gut. Cytidine deaminase is concentrated in the liver and intravenous doses show biphasic elimination with half lives of approximately 10 minutes and 1-3 hours.

After 24 hours 80% of a dose has been eliminated either as the inactive metabolite or as the unchanged cytarabine, mostly in urine but some in bile.

CSF levels of 50% of plasma levels are achieved with intravenous infusion. Intrathecal dosing results in slower elimination ($T_{1/2}$ 2-11 hours).

Cytarabine is rapidly and widely distributed into tissues, crosses the blood brain barrier and also the placenta.

Indication/Usage

Cytarabine may be used alone or in combination with other chemotherapeutic agents. It is indicated for induction of remission of leukaemia, particularly for acute myeloid leukaemia, in adults and children.

Cytrabine has been used for remission induction in acute lymphocytic leukaemia, chronic myeloid leukaemia and erythroleukaemia; and in the treatment and maintenance therapy of meningeal leukaemia and meningeal neoplasms.

Dosage and Administration

Administration

Being orally inactive, cytarabine is administered by a variety of parenteral routes: subcutaneously, intravenously either as a bolus "push" or as a continuous infusion, or intrathecally.

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

Thrombophlebitis has occurred at the site of drug injection or infusion in some patients. Pain and inflammation at subcutaneous injection sites are rare. Subcutaneous injection sites should be rotated around the areas of body fat: the abdomen, thighs and flank region. The drug is generally well tolerated in most instances.

Higher total doses can be better tolerated when administered by rapid IV injection as compared to slow infusion. Such a phenomenon can be explained by the rapid inactivation of the drug and the brief exposure of susceptible normal neoplastic cells to significant levels after rapid injection.

Normal and neoplastic cells appear to respond in almost parallel manner to these two modes of administration and no distinct advantage has been established for either.

Clinical experience to date indicates that success with cytarabine therapy depends more on adeptness in modifying day-to-day dosage to obtain maximum leukaemic cell kill with tolerable toxicity, than on the fundamental treatment protocol selected at the start of therapy. Toxicity necessitating dosage modification almost always occurs.

The potency of Cytarabine is retained for 24 hours at 2°C - 8°C in the following IV fluids:
1. Water for injection
2. Glucose 5% in water
3. Sodium Chloride 0.9%

Although stability of Cytarabine is well retained for 24 hours in intravenous vehicles noted above, it is recommended that as with all intravenous admixtures, dilution should be made just prior to administration and the resulting solution used within 24 hours.

Dosage:

Dosage of cytarabine must be based on the clinical and haematological response and tolerance of the patient so as to obtain optimum therapeutic results with minimum adverse effects. Even though higher total doses of cytarabine can be given by IV injection compared to continuous IV infusion with similar haematologic toxicity, the most effective dosage schedule and method of administration are yet to be established. Moreover, cytarabine is often used in combination with other cytotoxic drugs, thereby necessitating dose modification of cytarabine and other chemotherapeutic agents, and the method as well as the sequence of administration.
Following is an outline of dosage schedules for cytarabine therapy as reported in the literature.

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

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

Cytarabine combination therapy:
Before a combined chemotherapy protocol is instituted, the clinician should be familiar with current literature, precautions, contraindications, adverse reactions and warnings applicable to all the drugs involved in the protocol.

Cytarabine, Daunorubicin
Cytarabine: 100 mg/m^2/day, continuous IV infusion (days 1-7)
Daunorubicin: 45 mg/m^2/day, IV push (days 1-3)

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

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

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

Cytarabine, Doxorubicin
Cytarabine: 100 mg/m^2/day, continuous IV infusion (days 1-10)
Doxorubicin: 30 mg/m^2/day, IV infusion over 30 minutes (days 1-3)

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

Cytarabine, Doxorubicin, Vincristine, Prednisolone
Cytarabine: 100 mg/m^2/day, continuous IV infusion (days 1-7)
Doxorubicin: 30 mg/m^2/day, IV infusion (days 1-3)
Vincristine: 1.5 mg/m^2/day, IV infusion (days 1, 5)
Prednisolone: 40 mg/m^2/day, IV infusion every 12 hours (days 1-5)
Additional courses (complete or modified) as required at 2-4 week intervals if leukaemia is persistent.

Cytarabine, Daunorubicin, Thioguanine, Prednisone, Vincristine
Cytarabine: 100 mg/m^2/day, IV every 12 hours (days 1-7)
Daunorubicin: 70 mg/m^2/day, IV infusion (days 1-3)
Thioguanine: 100 mg/m^2 orally every 12 hours (days 1-7)
Prednisone: 40 mg/m^2/day, orally (days 1-7)
Vincristine: 1 mg/m^2/day, IV infusion (days 1, 7)

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

Maintenance of Acute Myelocytic Leukaemia (AML) in adults:
Maintenance programs are generally modifications of induction programs. Similar schedules of drug therapy to those used for induction are normally employed. Most programs have a greater interval between courses of therapy during remission maintenance.

Induction and maintenance of Acute Myelocytic Leukaemia (AML) in children:
Childhood AML has been shown to respond better than adult AML given similar regimens. Where the adult dosage is given in terms of body weight or surface area, the paediatric dosage may be calculated on the same basis, being adjusted on the consideration of such factors as age, body weight or body surface area.

Acute Lymphocytic Leukaemia (ALL):
Dosage schedules used in ALL are normally similar to those used in AML with some modifications.

Intrathecal use in Meningeal Leukaemia:
Cytarabine has been used intrathecally in acute leukaemia in doses ranging from 5 mg/m^2 to 75 mg/m^2 of body surface area. The frequency of administration varied from once a day for 4 days to once every 4 days. The most frequently used dose was 30 mg/m^2 every 4 days until cerebrospinal fluid findings were normal, followed by one additional treatment. The dosage schedule is usually governed by the type and severity of central nervous system manifestations and the response to previous therapy.

Dosage modification:

Suspension or modification of cytarabine therapy should be considered at the appearance of signs of serious haematologic depression, for example, if the polymorphonuclear granulocyte count falls below 1000/mm^3 or the platelet count falls below 50,000/mm^3. Such guidelines may be modified, depending on signs of toxicity in other systems and on the speed of fall in levels of formed blood elements. Therapy should be recommended when definite signs of bone marrow recovery appear and the above granulocyte and platelet levels are attained. If therapy is withheld until peripheral counts of blood elements return to normal, cytarabine may be ineffective.

Cytarabine Injection is a ready to use solution with a concentration of 100 mg/mL. It is suitable for intravenous use and in small volumes may also be used subcutaneously. Cytarabine injection 100 mg/mL is hypertonic and therefore unsuitable for intrathecal use unless diluted appropriately.

Contraindication

Cytarabine is contraindicated in patients with known hypersensitivity to the drug. Therapy with cytarabine should not be considered in patients with pre-existing drug-induced bone marrow suppression, unless in the opinion of the physician the potential benefits outweigh the hazards. Cytarabine should not be used in the management of non-malignant disease, except for immunosuppression.

Warnings & Precaution

Cytarabine is a potent bone marrow suppressant. Patients receiving the drug should be kept under close medical supervision. Leucocyte and platelet counts should be performed frequently and daily during induction. One case of anaphylaxis that resulted in cardiopulmonary arrest and necessitated resuscitation has been reported. This occurred immediately after intravenous cytarabine was administered.

Severe and at times fatal central nervous system (CNS), gastrointestinal (GI) and pulmonary toxicity (different from that seen with conventional therapy regimens of dosage schedules). These reactions include reversible corneal toxicity; cerebral and cerebellar dysfunction, usually reversible; severe gastrointestinal ulceration including pneumatosis cysteroides intestinalis, leading to peritonitis; sepsis and liver abscess; and pulmonary oedema.

Central Nervous System: Rarely, neurological effects such as severe spinal cord toxicity even leading to necrotising encephalopathy, quadriplegia and paralysis and blindness have been reported with cytosine arabinoside and have been predominantly associated with intrathecal administration. Isolated cases have also been reported with high intravenous doses during combination chemotherapeutic regimens.

Cytarabine has been shown to be mutagenic and carcinogenic in animals.

Cytarabine should only be used under the constant supervision by physicians experienced in therapy with cytotoxic agents. Hyperuricaemia secondary to lysis of neoplastic cells may occur in patients receiving cytarabine; serum uric acid concentrations should be monitored.

Periodic determinations of renal and hepatic functions and bone marrow should also be performed and the drug should be used with caution in patients with impaired hepatic function.

However, dosage reduction does not appear to be necessary in patients with impaired renal function. The human liver apparently detoxifies a substantial fraction of the administered dose. The drug should be used with caution and at a reduced dose when liver function is poor. Frequent platelet and leucocyte counts are mandatory. Therapy should be suspended or modified when drug-induced bone marrow depression results in a platelet count of less than 50,000 or a polymorphonuclear count of under 1000 per mm^3. Counts may continue to fall after the therapy has been discontinued and may reach lowest values after five to seven days. Therapy may be restarted when the bone marrow appears to be recovering on successive bone marrow studies. Therapy should not wait until the normal blood values are obtained to be re-initiated.

When intravenous doses are given quickly, patients may become nauseated and may vomit for several hours afterwards. The problem tends to be less severe when infused.

The safety of the drug has not been established in infants.

Interaction with other medicaments

i) Cardiac Glycosides
GI absorption of oral digoxin tablets may be substantially reduced in patients receiving combination chemotherapy regimens (including regimens containing cytarabine), possibly as a result of temporary damage to intestinal mucosa caused by the cytotoxic agents. Limited data suggest that the extent of GI absorption of digitoxin is not substantially affected by concomitant administration of combination chemotherapy regimens known to decrease absorption of digoxin.

ii) Anti-Infective Agents

One *in vitro* study indicates that cytarabine may antagonise the activity of gentamicin against *Klebsiella pneumoniae*. Limited data may suggest that cytarabine may antagonise the anti-infective activity of flucytosine, possibly by competitive inhibition of the anti-infective uptake by fungi.

Pregnancy and Lactation

Use in Pregnancy:
Cytarabine is teratogenic in some animal species. It should not be used in pregnant women (especially during the first trimester) or in those who may become pregnant, unless the

possible benefits outweigh the potential risks. Women who are, or become, pregnant during treatment with cytarabine should be informed of the risks.

Use in Lactation:
It is not known if cytarabine or its metabolite is distributed into breast milk, and it should not be used.

Side effects/Adverse Reactions

Haematological Effects:
The major adverse effect of cytarabine is the haematological toxicity. Myelosuppression is manifested by megaloblastosis, reticulocytopenia, thrombocytopenia and anaemia.

These appear to be more evident after high doses and continuous infusions; the severity depends on the dose of the drug and schedule of administration.

GI Effects:
Nausea and vomiting occur and are generally more frequent following rapid IV administration than with continuous IV infusion of the drug.

Diarrhoea, anorexia, oral and anal inflammation or ulceration and less frequently abdominal pain, sore throat, oesophagitis, oesophageal ulceration and gastrointestinal haemorrhage may also occur.

Other reported adverse effects of cytarabine include fever, rash, alopecia, skin ulceration, conjunctivitis, chest pain, urinary retention, dizziness, neuritis, neurotoxicity or neural toxicity and pain, cellulitis and thrombophlebitis (including irritation or sepsis) at the site of injection. Cytarabine has also been associated with renal dysfunction, hepatic dysfunction and jaundice in some patients. It has also been associated with freckling, skin, mucosal bleeding and joint pain.

A cytarabine reaction is characterised by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6-12 hours after administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are serious enough to warrant treatment, corticosteroids should be contemplated as well as continuation of cytarabine therapy.

Very rare cases of pericarditis have been reported.

Cases of pancreatitis have been reported.

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of dosage schedules). These reactions include reversible corneal toxicity; cerebral and cerebellar dysfunction, usually reversible; severe gastrointestinal ulceration including pneumatosis cysteriodes intestinalis, leading to peritonitis; sepsis and liver abscess; and pulmonary oedema.

Hyperuricaemia.

One case of anaphylaxis that resulted in cardiopulmonary arrest and necessitated resuscitation has been reported.
Central Nervous System: Rarely neurological effects such as severe spinal cord toxicity even leading to necrotising encephalopathy, quadriplegia and paralysis, and blindness have been reported.

Signs & Symptoms of overdose and Treatment

Cessation of therapy followed by management of ensuing bone marrow depression including whole blood or platelet transfusion and antibiotics as required.

Incompatibilities

Solutions of cytarabine have been reported to be incompatible with various drugs, i.e. carbenicillin sodium, cephalothin sodium, fluorouracil, gentamicin sulphate, heparin sodium, hydrocortisone sodium succinate, insulin-regular, methylprednisolone sodium succinate, nafacillin sodium, oxacillin sodium, penicillin G sodium. However, the incompatibility depends on several factors (e.g. concentrations of the drug, specific diluents used, resulting pH, temperature). Specialised references should be consulted for specific compatibility information.

Storage Conditions

To store below 30°C. Do not refrigerate. Keep the vial in the outer carton in order to protect from light. Keep out of the reach and sight of children.

Prepared infusions, in the recommended diluents, should be used immediately. Alternatively, the diluted infusion fluids may be stored at 2-8°C, protected from light, but portions remaining unused after 24 hours must be discarded.

Shelf life

24 months

Therapeutic Code (if any)

Antineoplastic Agent
ATC code: L01BC01

Dosage Forms and Packaging Available

ARASID INJECTION BP 100MG/ML (Cytarabine Injection BP 100 mg/ml) are available in pack size of 1ml, 5ml and 10ml. Each carton contains 1 glass vial.

Manufacturer

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Name and Address of Product Registration

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