SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cytarabine 100 mg/ml Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 100 mg of cytarabine.

Presentations	100 mg/1 ml	500 mg/5 ml	1 g/10 ml	2 g/20 ml
Amount cytarabine Present	100 mg	500 mg	1 g	2 g

For the full list of excipients see 6.1

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Cytarabine may be used alone or in combination with other antineoplastic agents. It is indicated alone or in combination for induction of remission and/or maintenance in patients with acute myeloid leukaemia, acute non-lymphoblastic leukaemias, acute lymphoblastic leukaemias, acute lymphocytic leukaemia, erythroleukaemia, blast crises of chronic myeloid leukaemia, diffuse histiocytic lymphomas (non-Hodgkin's lymphomas of high malignancy), meningeal leukaemia and meningeal neoplasms. Clinicians should refer to the current literature on combination therapy before initiating treatment.

4.2 Posology and method of administration

Posology

Cytarabine Injection can be diluted with Sterile Water for Injections BP, Glucose Intravenous Infusion BP or Sodium Chloride Intravenous Infusion BP. 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.

Remission Induction: Adults

Continuous dosing: The usual dose in leukaemia is 2 mg/kg by rapid intravenous injection daily for ten days. If after ten days neither therapeutic response nor toxicity has been observed, the dose may be increased to 4 mg/kg until a therapeutic response or toxicity is evident. Daily blood counts should be taken. Almost all patients can be carried to toxicity with these doses.

Alternatively, 0.5 to 1 mg/kg may be infused daily in 1-24 hours for ten days, and then at a rate of 2 mg/kg/day until toxicity is observed. Continue to toxicity or until remission occurs. Results from one hour infusions have been satisfactory in the majority of patients.

Intermittent dosing: Cytarabine may be given as intermittent intravenous doses of 3-5 mg/kg daily, for five consecutive days. This course of treatment can be repeated after an interval of 2 to 9 days and repeated until the therapeutic response or toxicity is exhibited.

Evidence of bone marrow improvement has been reported to occur 7-64 days after the beginning of therapy.

In general, if a patient shows neither remission nor toxicity after a trial period, then cautiously administered higher doses can be administered. Generally patients tolerate higher doses given by rapid intravenous injection rather than slow infusion.

As a single agent for induction of remissions in patients with acute leukaemia, cytarabine has been given in doses of 200 mg/m^2 by continuous intravenous infusion for five days at approximately 2 week intervals.

Maintenance therapy: To maintain remission, doses of 1 mg/kg may be given intravenously or subcutaneously, once or twice weekly.

Leukemic meningitis: Therapy for established meningitis employs a wide variety of dose regimens but a recommended total daily dose not exceeding 100 mg, alternating with methotrexate is recommended.

Myelosuppression, anaemia and thrombocytopenia occur almost to all patients given daily infusions or injections. Myelosuppression is biphasic and nadirs at 7-9 and 15-24 days. Evidence of bone marrow improvement may be expected 7-64 (mean 28) days after the beginning of treatment.

Paediatric population: Children appear to tolerate higher doses of cytarabine than adults, and where the range of doses is given, children should receive the higher dose.

Elderly: No data is available to suggest that a change in dose is necessary in the elderly. However, the elderly patient is more susceptible to toxic reactions and therefore particular attention should be paid to drug induced leukopenia, thrombocytopenia and anaemia.

<u>Method of administration</u>

Cytarabine 100 mg/ml Injection is a ready to use injection and can be administered by the intravenous and subcutaneous routes. **Cytarabine 100 mg/ml Injection should not be administered by the intrathecal route due to the slight hypertonicity of this formulation. (See section 4.8).**

4.3 Contraindications

Hypersensitivity to cytarabine or to any of the excipients listed in 6.1.

Anaemia, leukopenia and thrombocytopenia of non-malignant aetiology (e.g. bone marrow aplasia), unless the benefits outweigh the risk.

Degenerative and toxic encephalopathies, especially after the use of methotrexate or treatment with ionizing radiation.

During pregnancy, cytarabine should only be administrated on strict indication, where the benefits of the drug to the mother should be weighed against possible hazards to the foetus.

4.4 Special warnings and precautions for use

Cytarabine is a potent bone marrow suppressant. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression. Patients receiving the drug should be kept under close medical supervision. Leucocyte and platelet counts should be performed frequently and daily during induction. 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 haemorrhage secondary to thrombocytopenia).

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 cytarabine) has been reported following some experimental cytarabine dose schedules. These reactions include reversible corneal toxicity; cerebral and cerebellar dysfunction, usually reversible; somnolence; convulsion; severe gastrointestinal ulceration including pneumatises cysteroides intestinalis, leading to peritonitis; sepsis and liver abscess; and pulmonary oedema.

The risk of CNS toxicity increases if high dose cytarabine is given in combination with another CNS toxic treatment such as radiation therapy or in patients who have previously had CNS treatment as chemotherapy intrathecally. 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 (see section 4.8).

Delayed progressive ascending paralysis resulting in death has been reported in children with AML following intravenous cytarabine at conventional doses in combination with other drugs.

Cytarabine has been shown to be mutagenic and carcinogenic in animals. The possibility of a similar effect should be borne in mind when designing the long-term management of the patient.

Cytarabine should only be used under the constant supervision by physicians experienced in therapy with cytotoxic agents. Hyperuricemia secondary to rapid lysis of neoplastic cells may occur in patients receiving cytarabine; serum uric acid concentrations should be monitored. The physician should be prepared to use such supportive and pharmacological measures as may be necessary to control this problem.

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 polymorph nuclear 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. If treatment is not resumed before blood values return to normal, the disease can get out of control.

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.

Abdominal tenderness (peritonitis) and guaiac positive colitis, 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 non-operative medical management.

Concurrent granulocyte-transfusion should be avoided as severe respiratory insufficiency has been reported.

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.

High dose therapy

Peripheral motor and sensory neuropathies after consolidation with high doses of cytarabine, daunorubicin, and asparaginase have occurred in adult patients with acute non lymphocytic leukaemia.

Patients treated with high doses of cytarabine should be observed for neuropathy since dose adjustments may be needed to avoid irreversible neurologic disorders.

Severe and sometimes fatal pulmonary toxicity, adult respiratory distress syndrome, and pulmonary edema have occurred following high dose schedules with cytarabine therapy. 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.

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

Excipient information
Cytarabine 100 mg/ml Injection contains less than 1 mmol sodium (23 mg) in each vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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. Reversible decreases in steady-state plasma digoxin concentrations and renal glycoside excretion were observed in patients receiving beta-acetyl digoxin and chemotherapy regimens containing cyclophosphamide, vincristine and prednisone with or without cytarabine or procarbazine. 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. 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.

Anti-Infective Agents
One *in vitro* study indicates that cytarabine may antagonise the activity of gentamicin against *Klebsiella pneumoniae*. In patients on cytarabine being treated with gentamicin for a *K.pneumoniae* infection, a lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.

5-Fluorocytosine:
5-Fluorocytosine should not be administered with cytarabine as the therapeutic efficacy of 5-Fluorocytosine has been shown to be abolished during such therapy.

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

Methotrexate

There is evidence of pharmacodynamic interaction between methotrexate and cytarabine leading to encephalopathy.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Due to the potential for genotoxicity, female patients of reproductive potential should be advised to use highly effective contraception during treatment and for 6 months after the last dose of cytarabine.

Due to the potential for genotoxicity, male patients with female partners of reproductive potential should be advised to use highly effective contraception during treatment and for 3 months after the last dose of cytarabine.

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 who may become, pregnant during treatment with cytarabine should be informed of the risks.

Breast-feeding

It is not known if cytarabine or its metabolite is distributed into breast milk. Lactating women should discontinue breast-feeding for the duration of cytarabine therapy and for at least 1 week after the last dose of cytarabine.

Fertility

Fertility studies to assess the reproductive toxicity of cytarabine have not been conducted. Gonadal suppression, resulting in amenorrhea or azoospermia, may occur in patients taking cytarabine therapy, especially in combination with alkylating agents. In general, these effects appear to be related to dose and length of therapy and may be irreversible. Cytarabine has a mutagenic potential which could induce chromosomal damage in the human spermatozoa.

4.7 Effects on ability to drive and use machines

No documented effect on ability to drive or operate machinery.

Nevertheless, patients receiving chemotherapy may have an impaired ability to drive or operate machinery and should be warned of the possibility and advised to avoid such tasks if so affected.

4.8. Undesirable Effects

The following adverse events have been reported in association with cytarabine therapy. Frequencies are defined using the following convention:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data)

Undesirable effects from cytarabine are dose-dependent. Most common are gastrointestinal undesirable effects. Cytarabine is toxic to the bone marrow, and causes haematological undesirable effects.

Infections and infestations
Uncommon: Sepsis (immunosuppression)

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Uncommon: Lentigo

Blood and lymphatic system disorders
Common: Anaemia, megaloblastosis, leukopenia, thrombocytopenia
Not known: Reticulocytopenia, neutropenia, febrile neutropenia

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.

Gastrointestinal disorders
Common: Dysphagia, abdominal pain, nausea, vomiting, diarrhoea, oral/anal inflammation or ulceration
Uncommon: Oesophagitis, oesophageal ulceration, pneumatosis cystoides intestinalis, necrotising colitis, peritonitis
Not known: Gastrointestinal haemorrhage, pancreatitis

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

Skin and subcutaneous tissue disorders
Common: Reversible undesirable effects to the skin, such as erythema, bullous dermatitis, urticaria, vasculitis, alopecia
Uncommon: skin ulceration, pruritus, burning pain of palms and soles
Not known: Rash, freckling, skin bleeding, Palmar-plantar erythrodysaesthesia syndrome, Neutrophilic eccrine hidradenitis, Auricular erythema (“Ara-C ears”)

Renal and urinary disorders
Common: Renal impairment, urinary retention
Not known: Renal dysfunction

General disorders and administration site conditions
Common: Fever, thrombophlebitis at the site of injection
Uncommon: Cellulitis at the injection site
Not known: Chest pain, irritation or sepsis at the injection site, mucosal bleeding

Cardiac disorders
Uncommon: Pericarditis
Very rare: Arrhythmia
Not Known: Sinus bradycardia

Hepatobiliary disorders
Common: Reversible effects on the liver with increased enzyme levels

Not known: Hepatic dysfunction and jaundice

Metabolism and nutrition disorders
Common: Anorexia, hyperuricemia
One case of anaphylaxis that resulted in cardiopulmonary arrest and necessitated resuscitation has been reported (see section 4.4 Special warnings and precautions for use).

Nervous system disorders
Common: At high doses cerebellar or cerebral influence with deterioration of the level of consciousness, dysarthria, nystagmus
Uncommon: Headache, peripheral neuropathy, paraplegia at intrathecal administration
Not known: Dizziness, neuritis or neural toxicity and pain, neurotoxicity rash

Eye disorders
Common: Reversible haemorrhagic conjunctivitis (photophobia, burning, visual disturbance, increased lacrimation), keratitis
Not known: Conjunctivitis

Respiratory, thoracic and mediastinal disorders
Uncommon: Pneumonia, dyspnoea, sore throat

Musculoskeletal and connective tissue disorders
Uncommon: Myalgia, joint pain

A cytarabine syndrome (immunoallergic effect) is characterised by fever, myalgia, bone pain, occasionally chest pain, exanthema, maculopapular rash, conjunctivitis, nausea 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. If treatment is effective, therapy with cytarabine may be continued.

Adverse effects due to high dose cytarabine treatment, other than those seen with conventional doses include:

Blood and lymphatic system disorders
Hematological toxicity has been seen as profound pancytopenia which may last 15-25 days along with more severe bone marrow aplasia than that observed at conventional doses.

Nervous system disorders
After treatment with high doses of cytarabine, symptoms of cerebral or cerebellar influence like personality changes, affected alertness, dysarthria, ataxia, tremor, nystagmus, headache, confusion, somnolence, dizziness, coma, convulsions, etc. appear in 8-37 % of treated patients. The incidence in elderly (>55 years) may be even higher. Other predisposing factors are impaired liver and renal function, previous CNS treatment (e.g., radiotherapy) and alcohol abuse. CNS disturbances are in the most cases reversible.

The risk of CNS toxicity increases if the cytarabine treatment, given as high dose IV, is combined with another CNS toxic treatment such as radiation therapy or high dose of a cytotoxic agent.

Eye disorders
Reversible corneal lesion and haemorrhagic conjunctivitis have been described. These phenomena can be prevented or decreased by installation of corticosteroid eye drops.

Gastrointestinal disorders
Especially in treatment with high doses of cytarabine, more severe reactions may appear in addition to common symptoms. Intestinal perforation or necrosis with ileus and peritonitis have been reported. Pancreatitis has also been observed after high-dose therapy.

Hepatobiliary disorders
Liver abscesses, hepatomegaly, Budd-Chiari-syndrome (hepatic venous thrombosis), and hyperbilirubinemia have been observed after high-dose therapy.

Respiratory, thoracic and mediastinal disorders
Clinical signs as present in pulmonary oedema/ARDS may develop, particularly in high-dose therapy. The reaction is probably caused by an alveolar capillary injury. It is difficult to make an assessment of frequencies (stated as 10-26 % in different publications), since the patients usually have been in relapse where other factors may contribute to this reaction.

Reproductive system and breast disorders
Amenorrhoea and azoospermia

Others
Following cytarabine therapy, cardiomyopathy and rhabdomyolysis have been reported.

The gastrointestinal undesirable effects are reduced if cytarabine is administered as infusion. Local glucocorticoids are recommended as prophylaxis of haemorrhagic conjunctivitis.

One case of anaphylaxis that resulted in cardiopulmonary arrest and necessitated resuscitation has been reported (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

There is no specific antidote for cytarabine overdose. Cessation of therapy followed by management of ensuing bone marrow depression including whole blood or platelet transfusion and antibiotics as required.

Twelve doses of 4.5 g/m^2 by IV infusion over one hour every 12 hours induces irreversible and fatal central nervous system toxicity.

Cytarabine may be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pyrimidine analogues, ATC code: L01BC01

Mechanism of action

Cytarabine (ARA-C) 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.

5.2 Pharmacokinetic properties

Absorption
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.

Elimination
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.

Distribution
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.

5.3. Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections
Hydrochloric Acid (for pH adjustment)
Sodium Hydroxide (for pH adjustment)

6.2. 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.

6.3 Shelf life

Before use: 18 months

In use: Chemical and physical in-use stability has been demonstrated for 7 days at room temperature.

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

6.4 Special precautions for storage

Do not refrigerate or freeze.

Do not store above 25°C. Keep container in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Clear Type I glass vial with rubber stopper
Clear Type I glass Onco-Tain® vial with rubber stopper
Clear Type I glass Onco-Vial® with rubber stopper

Pack sizes 1's, 5's, 10's and 20's.

Not all presentations and pack sizes may be marketed.

6.6 Special precautions for disposal

Prior to use, vials of Cytarabine 100mg/ml Injection must be warmed to 55°C, for 30 minutes, with adequate shaking, and allowed to cool to room temperature.

Use in the paediatric population

No special requirements

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

7 MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Walton Oaks
Walton-On-The-Hill
Dorking Road
Tadworth
Surrey
KT20 7NS
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 04515/0057

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