Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cytarabine 100 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 100 mg of cytarabine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear, colourless, sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Alone or in combination for the induction of clinical remission and/or maintenance therapy in patients with acute myeloid leukaemia, acute non-lymphoblastic leukaemias, lymphoblastic leukaemia, erythroleukaemia, blast crises of chronic myeloid leukaemia and non-Hodgkin lymphoma.

4.2 Posology and method of administration

Posology

The following doses are given as a guide, but the clinician should consult relevant protocols for the appropriate dosage of cytarabine and other antineoplastic agents given in combination. Most doses are given in mg/kg but may be converted to doses related to surface area by the use of standard nomograms.

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 IV 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 IV Infusion for five days at approximately 2 week intervals.

Maintainance Therapy: To maintain remission, doses of 1-1.5 mg/kg may be given intravenously or subcutaneously, once or twice weekly.

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 leucopenia, thrombocytopenia and anaemia.

Method of administration
May be administered intravenously (IV) or subcutaneously (SC) only.

This product is hypertonic and must not be administered by the intrathecal route.

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

4.3 Contraindications

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

Anaemia, leucopenia and thrombocytopenia of non-malignant etiology (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 (see section 4.6).

4.4 Special warnings and precautions for use

Cytarabine should only be used with great caution in patients who have recently received radiotherapy or other cytotoxic agents.

Cytarabine should only be administered with caution under the direction of a specialist oncology service having the facilities for regular monitoring of clinical biochemical and haematological effects during and after administration.

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 must be kept under close medical supervision. Leucocyte and platelet counts should be performed frequently and daily during induction. Periodic bone marrow examinations should be conducted; the examinations should be frequent after blast cells have disappeared from the peripheral blood. Facilities should be available for management of complications of possibly fatal bone marrow suppression (infection resulting from granulocytopenia and other impaired body defences and haemorrhage secondary to thrombocytopenia).
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 cubic mm. 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 unti l the normal blood values ar e obtained to be re- initiated . If treatment is not resumed before blood values return to normal, the disease can get out of control.

One case of anaphylaxis that resulted in acute cardiopulmonary arrest and necessitated resuscitation has been reported. This occurred immediately after intravenous cytarabine was administered.

Periodic determinations of bone marrow, renal and hepatic functions should be performed, and the drug should be used with caution and at reduced dosages 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.

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

Hyperuricaemia prophylaxis is concurrently essential. 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 pharmacological measures as may be necessary to control this problem.

Cytarabine has been shown to be mutagenic and carcinogenic in animals. The possibility of the above effects should be considered when cytarabine is used in long-term management of patients.

Immunosuppressant effects/Increased susceptibility to infections
Administration of live or live-attenuated vaccines in patientsimmunocompromised 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.

Abdominal tenderness (peritonitis) and guaiac positive colitis, with concurrent neutropenia and thrombocytopenia, have been reported in patients treated with conventio nal doses of cytarabine in combination with other drugs. Patients have responded to nonoperative medical management.

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.

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 leuk emia.

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

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.

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

Safety in infants has not been established.

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: Gastro-intestinal 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-acetyldigoxin and chemotherapy regimens containing cyclophosphamide, vincristine and prednisone with or without cytarabine or procarbazine.

Limited data suggest that the extent of gastro-intestinal absorption of digitoxin is not substantially affected by concomitant administration of combination chemotherapy regimens known to decrease absorption of digoxin. 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.

Cytotoxic Antibiotics:
Increased toxicity may occur following the concurrent use of cytarabine and idarubicin.

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. 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.

Immunosuppressive agents:
Due to the immunosuppresive 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 has been shown to be teratogenic in some animal species. The use of cytarabine in women who are, or who may become, pregnant should be undertaken only after due consideration of the potential benefits and hazards.

Breast-feeding
It is not known whether cytarabine or metabolites are excreted in the breast milk. This product should not be administered to mothers who are breast-feeding.

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 for the duration of cytarabine therapy and for at least one week after the last dose or to discontinue the drug, taking into account the importance of the drug to the mother.

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

Cytarabine has no effect on intellectual function or psychomotor performance. 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.

Cytarabine Syndrome (immunoallergic effect): This 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.

Infections and infestations
Uncommon: sepsis (immunosuprression), pneumonia

Blood and the lymphatic system disorders
Very common: Myelosuppression, neutropenia, reticulocytopenia
Common: Thrombocytopenia, anaemia, megaloblastosis, leucopenia
*Not known:*Febrile neutropenia

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

Immune system disorders
Very rare: Anaphylaxis

Metabolism and nutrition disorders

Common: Anorexia, hyperuricaemia secondary to lysis of neoplastic cells

Nervous system disorders
Common: At high doses cerebellar or cerebral influence with deterioration of the level of consciousness, dysarthria, nystagmus, dizziness, neuritis or neural toxicity and pain
Uncommon: Headache, peripheral neuropathy and paraplegia at intrathecal administration

Very rare: Severe spinal cord toxicity (even leading to necrotising encephalopathy, quadriplegia, paralysis and blindness)

Severe spinal cord toxicity is predominantly associated with intrathecal administration, but isolated cases have also been reported with high intravenous doses during combination chemotherapeutic regimens. Other isolated neurotoxicities have been reported.

Eye disorders
Very common: Conjunctivitis (high dose therapy)
Common: Reversible haemorrhagic conjunctivitis (photophobia, burning, visual disturbance, increased lacrimation), keratitis

Cardiac disorders
Uncommon: Pericarditis
Very rare: Arrhythmia

Not Known: Sinus bradycardia

Respiratory, thoracic and mediastinal disorders.
Uncommon: Dyspnoea, sore throat

Gastrointestinal disorders
Very common: Gastrointestinal haemorrhage
Common: Dysphagia, nausea, vomiting, diarrhoea, oral and anal inflammation or ulceration, abdominal pain,
Uncommon: Oesophagitis, oesophageal ulceration, pneumatosis cystoides intestinalis, necrotising colitis, peritonitis
Very rare: Pancreatitis

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 cytarabine is infused.

Hepatobiliary disorders
Very common: Hepatic dysfunction, jaundice
Common: Reversible effects on the liver with increased enzyme levels
Not known: Hyperbilirubinemia

Skin and subcutaneous tissue disorders
Very common: Rash (erythema bullosa-like skin reactions), skin bleeding
*Common:*Reversible undesirable effects to the skin, such as erythema, bullous dermatitis, urticaria, vasculitis, alopecia (high dose therapy)
Uncommon: Lentigo, skin ulceration, pruritus, painful redness and blistering of the hands and the soles of the feet (high dose therapy)
Not known: Freckling, neutrophilic eccrine hidradenitis, auricular erythema ("Ara-C ears")

Musculoskeletal and connective tissue disorders
Uncommon:Joint pain, myalgia

Renal and urinary disorders
Common: renal dysfunction, urinary retention

General disorders and administration site conditions
Very common: Chest pain, mucosal bleeding; irritation or sepsis at the site of injection.
Common: Fever, thrombophlebitis at the site of injection.
Uncommon: Cellulitis at the site of injection.

Adverse effects due to high dose cytarabine treatment, other than those seenwith conventional doses include:
Severe and at times fatal CNS, gastro-intestinal and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine) have been reported following experimental cytarabine dosage schedules. These reactions include reversible corneal toxicity; cerebral and cerebellar dysfunction, usually reversible; somnolence, convulsion, severe gastrointestinal ulceration, including pneumatosis cysteroides intestinalis, leading to peritonitis; sepsis and liver abscess; and pulmonary oedema.

Blood and lymphatic system disorders
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 i.v.- 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.

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.

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 and Budd-Chiari-syndrome (hepatic venous thrombosis) have been observed after high-dose therapy.

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 hemorrhagic conjunctivitis.

Amenorrhoea and azoospermia.

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 HPRA Pharmacovigilance. Website: www.hpra.ie.

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/m2 by IV infusion over one hour every 12 hours induces irreversible and fatal central nervous system toxicity.

Cytarabine may be removed by hemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pyrimidine analogues, ATC code: L01BC01

Mechanism of action

A pyrimidine anti-metabolite myelo-suppressant converted by phosphorylation to its active form.

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 IV infusion.

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 the data already included in other sections of the Summary of Product Characteristics.

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

Unopened: 18 months.

Chemical and physical in-use stability has demonstrated that the product is stable for 14 days at 20-21°C.

From a microbiological point of view, unless the method of opening/ reconstitution/ dilution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

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

Do not refrigerate or freeze.

For in-use storage precautions, see section 6.3.

6.5 Nature and contents of container

100 mg/1ml vials:
Clear, conventional or ONCO -TAIN®, Type I glass vials with rubber stopper.
Packs of 5 vials.

1g/10ml vials:
Clear, conventional or ONCO-TAIN®, Type I glass vial with rubber stopper.
Single vial packs.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. Discard any unused contents.

See section 4.2 for compatible diluents and instructions on administration.

Reference should also be made to local policy guidelines on the safe handling of cytotoxic agents.

If a precipitate has formed as a result of exposure to low temperature, re-dissolve 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.

Use immediately following warming and cooling of the vial. Further storage is not recommended after warming.

Cytotoxic Handling Guidelines

Administration:

Should be administered by, or under the direct supervision of, a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

Preparation (Guidelines):

1.Chemotherapeutic agents should be prepared for administration only by professionals trained in the safe use of the preparation.

2.Operations such as dilution and transfer to syringes should be carried out only in the designated area.

3.The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.

4.Pregnant personnel are advised not to handle chemotherapeutic agents.

Contamination:

(a)In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat the transient stinging of skin. Medical advice should be sought if the eyes are affected.

(b)In the event of spillage, operators should put on gloves and mop up the spilled material with a sponge kept in the area for that purpose. Rinse the area twice with water. Put all solutions and sponges into a plastic bag and seal it.

Use in the paediatric population

No special requirements.

Disposal:

Syringes, container, absorbent materials, solution and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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